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(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF BREAST CANCER

SYN18C6 NORTHERN BLOT

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1.35 kb →

0.24 kb →

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as breast cancer, are disclosed. Compositions may comprise one or more breast tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a breast tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as breast cancer. Diagnostic methods based on detecting a breast tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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ning of each regular issue of the PCT Gazette.*

COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF BREAST CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of
5 cancer, such as breast cancer. The invention is more specifically related to polypeptides
comprising at least a portion of a breast tumor protein, and to polynucleotides encoding
such polypeptides. Such polypeptides and polynucleotides may be used in
compositions for prevention and treatment of breast cancer, and for the diagnosis and
monitoring of such cancers.

10 BACKGROUND OF THE INVENTION

Breast cancer is a significant health problem for women in the United
States and throughout the world. Although advances have been made in detection and
treatment of the disease, breast cancer remains the second leading cause of cancer-
related deaths in women, affecting more than 180,000 women in the United States each
15 year. For women in North America, the life-time odds of getting breast cancer are one
in eight.

No vaccine or other universally successful method for the prevention or
treatment of breast cancer is currently available. Management of the disease currently
relies on a combination of early diagnosis (through routine breast screening procedures)
20 and aggressive treatment, which may include one or more of a variety of treatments
such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of
treatment for a particular breast cancer is often selected based on a variety of prognostic
parameters, including an analysis of specific tumor markers. *See, e.g., Porter-Jordan
and Lippman, Breast Cancer 8:73-100 (1994).* However, the use of established
25 markers often leads to a result that is difficult to interpret, and the high mortality
observed in breast cancer patients indicates that improvements are needed in the
treatment, diagnosis and prevention of the disease.

Accordingly, there is a need in the art for improved methods for the
treatment and diagnosis of breast cancer. The present invention fulfills these needs and
30 further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as breast cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a breast tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477 479, 484, 486 and 489; (b) variants of a sequence recited in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489; and (c) complements of a sequence of (a) or (b). In specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 176, 179, 181, 469-473, 475, 485, 487 and 488, and variants thereof.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a breast tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, immunogenic compositions, or vaccines for prophylactic or therapeutic use are provided. Such compositions comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a breast tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as

described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, immunogenic compositions, or vaccines, are
5 provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that
comprise at least one polypeptide as described above, as well as polynucleotides
10 encoding such fusion proteins. Exemplary fusion proteins according to the present invention comprise a first amino acid portion and a second amino acid portion wherein the first amino acid portion includes 9 or more contiguous amino acids from
mammaglobin as depicted by amino acids 1-93 of SEQ ID NO: 493; wherein the
second amino acid portion includes 9 or more contiguous amino acids from B726P as
15 depicted by SEQ ID NO: 475, SEQ ID NO: 469, or SEQ ID NO: 176; and wherein the first amino acid portion is connected to either the amino terminal or carboxy-terminal end of the second amino acid portion.

Still further embodiments of the present invention provide fusion
proteins
20 wherein said first amino acid portion is selected from the group consisting of
IDELKECFLNQTDETLSNVE (amino acids 59-78 of SEQ ID NO: 493);
TTNAIDELKECFLNQ (amino acids 55-69 of SEQ ID NO: 493);
SQHCYAGSGCPLLENVISKTI (amino acids 13-33 of SEQ ID NO: 493);
EYKELLQEFIDDNATTNAID (amino acids 41-60 of SEQ ID NO: 493);
25 KLLMVLMLA (amino acids 2-10 of SEQ ID NO: 493); QEFIDDNATTNAI (amino acids 47-59 of SEQ ID NO: 493); and LKECFLNQTDETL (amino acids 62-74 of SEQ ID NO: 493).

Alternative embodiments provide fusion proteins wherein the second
amino acid portion includes 9 or more contiguous amino acids encoded by (1) the
30 combined upstream and downstream open reading frame (ORF) of B726P as depicted
in SEQ ID NO: 475; (2) the upstream ORF of B726P as depicted in from SEQ ID NO:

469; and (3) the downstream ORF of B726P as depicted in SEQ ID NO: 176. Fusion proteins according to the present invention may also comprise a second amino acid portion that includes 9 or more contiguous amino acids from the amino acid sequence depicted by amino acids 1-129 of SEQ ID NO: 475. Still additional exemplary fusion proteins are depicted herein by SEQ ID NO: 493; SEQ ID NO: 494; and SEQ ID NO: 495.

Fusion proteins are provided wherein the mammaglobin amino acid portion is connected to the amino-terminus of the B726P amino acid portion while other fusion proteins are provided wherein the mammaglobin amino acid portion is connected to the carboxy-terminus of the B726P amino acid portion. The connection between the mammaglobin amino acid portion and the B726P portion may be a covalent bond. Additionally, a stretch of amino acids either unrelated or related to either mammaglobin and/or B726P may be incorporated between or either amino- or carboxy-terminal to either the mammaglobin and/or B726P amino acid portion.

The present invention also provides isolated polynucleotides that encode any of the fusion proteins that are specifically disclosed herein as well as those fusion proteins that may be accomplished with routine experimentation by the ordinarily skilled artisan.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Compositions are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a composition as recited above. The patient may be afflicted with breast cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological

sample with T cells that specifically react with a breast tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the
5 development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a breast tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide
10 encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for
15 inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide
20 comprising at least an immunogenic portion of a breast tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the
25 patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that
30 binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a

cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be breast cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as
5 monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All
10 references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Fig. 1 shows the results of a Northern blot of the clone SYN18C6 (SEQ ID NO: 40).

- 15 SEQ ID NO: 1 is the determined cDNA sequence of JBT2.
SEQ ID NO: 2 is the determined cDNA sequence of JBT6.
SEQ ID NO: 3 is the determined cDNA sequence of JBT7.
SEQ ID NO: 4 is the determined cDNA sequence of JBT10.
SEQ ID NO: 5 is the determined cDNA sequence of JBT13.
20 SEQ ID NO: 6 is the determined cDNA sequence of JBT14.
SEQ ID NO: 7 is the determined cDNA sequence of JBT15.
SEQ ID NO: 8 is the determined cDNA sequence of JBT16.
SEQ ID NO: 9 is the determined cDNA sequence of JBT17.
SEQ ID NO: 10 is the determined cDNA sequence of JBT22.
25 SEQ ID NO: 11 is the determined cDNA sequence of JBT25.
SEQ ID NO: 12 is the determined cDNA sequence of JBT28.
SEQ ID NO: 13 is the determined cDNA sequence of JBT32.
SEQ ID NO: 14 is the determined cDNA sequence of JBT33.
SEQ ID NO: 15 is the determined cDNA sequence of JBT34.
30 SEQ ID NO: 16 is the determined cDNA sequence of JBT36.

- SEQ ID NO: 17 is the determined cDNA sequence of JBT37.
SEQ ID NO: 18 is the determined cDNA sequence of JBT51.
SEQ ID NO: 19 is the determined cDNA sequence of JBTT1.
SEQ ID NO: 20 is the determined cDNA sequence of JBTT7.
5 SEQ ID NO: 21 is the determined cDNA sequence of JBTT11.
SEQ ID NO: 22 is the determined cDNA sequence of JBTT14.
SEQ ID NO: 23 is the determined cDNA sequence of JBTT18.
SEQ ID NO: 24 is the determined cDNA sequence of JBTT19.
SEQ ID NO: 25 is the determined cDNA sequence of JBTT20.
10 SEQ ID NO: 26 is the determined cDNA sequence of JBTT21.
SEQ ID NO: 27 is the determined cDNA sequence of JBTT22.
SEQ ID NO: 28 is the determined cDNA sequence of JBTT28.
SEQ ID NO: 29 is the determined cDNA sequence of JBTT29.
SEQ ID NO: 30 is the determined cDNA sequence of JBTT33.
15 SEQ ID NO: 31 is the determined cDNA sequence of JBTT37.
SEQ ID NO: 32 is the determined cDNA sequence of JBTT38.
SEQ ID NO: 33 is the determined cDNA sequence of JBTT47.
SEQ ID NO: 34 is the determined cDNA sequence of JBTT48.
SEQ ID NO: 35 is the determined cDNA sequence of JBTT50.
20 SEQ ID NO: 36 is the determined cDNA sequence of JBTT51.
SEQ ID NO: 37 is the determined cDNA sequence of JBTT52.
SEQ ID NO: 38 is the determined cDNA sequence of JBTT54.
SEQ ID NO: 39 is the determined cDNA sequence of SYN17F4.
SEQ ID NO: 40 is the determined cDNA sequence of SYN18C6 (also
25 known as B709P).
SEQ ID NO: 41 is the determined cDNA sequence of SYN19A2.
SEQ ID NO: 42 is the determined cDNA sequence of SYN19C8.
SEQ ID NO: 43 is the determined cDNA sequence of SYN20A12.
SEQ ID NO: 44 is the determined cDNA sequence of SYN20G6.
30 SEQ ID NO: 45 is the determined cDNA sequence of SYN20G6-2.
SEQ ID NO: 46 is the determined cDNA sequence of SYN21B9.

- SEQ ID NO: 47 is the determined cDNA sequence of SYN21B9-2.
SEQ ID NO: 48 is the determined cDNA sequence of SYN21C10.
SEQ ID NO: 49 is the determined cDNA sequence of SYN21G10.
SEQ ID NO: 50 is the determined cDNA sequence of SYN21G10-2.
5 SEQ ID NO: 51 is the determined cDNA sequence of SYN21G11.
SEQ ID NO: 52 is the determined cDNA sequence of SYN21G11-2.
SEQ ID NO: 53 is the determined cDNA sequence of SYN21H8.
SEQ ID NO: 54 is the determined cDNA sequence of SYN22A10.
SEQ ID NO: 55 is the determined cDNA sequence of SYN22A10-2.
10 SEQ ID NO: 56 is the determined cDNA sequence of SYN22A12.
SEQ ID NO: 57 is the determined cDNA sequence of SYN22A2.
SEQ ID NO: 58 is the determined cDNA sequence of SYN22B4.
SEQ ID NO: 59 is the determined cDNA sequence of SYN22C2.
SEQ ID NO: 60 is the determined cDNA sequence of SYN22E10.
15 SEQ ID NO: 61 is the determined cDNA sequence of SYN22F2.
SEQ ID NO: 62 is a predicted amino acid sequence for SYN18C6 (also known as B709P).
SEQ ID NO: 63 is the determined cDNA sequence of B723P.
SEQ ID NO: 64 is the determined cDNA sequence for B724P.
20 SEQ ID NO: 65 is the determined cDNA sequence of B770P.
SEQ ID NO: 66 is the determined cDNA sequence of B716P.
SEQ ID NO: 67 is the determined cDNA sequence of B725P.
SEQ ID NO: 68 is the determined cDNA sequence of B717P.
SEQ ID NO: 69 is the determined cDNA sequence of B771P.
25 SEQ ID NO: 70 is the determined cDNA sequence of B722P.
SEQ ID NO: 71 is the determined cDNA sequence of B726P.
SEQ ID NO: 72 is the determined cDNA sequence of B727P.
SEQ ID NO: 73 is the determined cDNA sequence of B728P.
SEQ ID NO: 74-87 are the determined cDNA sequences of isolated
30 clones which show homology to known sequences.
SEQ ID NO: 88 is the determined cDNA sequence of 13053.

SEQ ID NO: 89 is the determined cDNA sequence of 13057.
SEQ ID NO: 90 is the determined cDNA sequence of 13059.
SEQ ID NO: 91 is the determined cDNA sequence of 13065.
SEQ ID NO: 92 is the determined cDNA sequence of 13067.
5 SEQ ID NO: 93 is the determined cDNA sequence of 13068.
SEQ ID NO: 94 is the determined cDNA sequence of 13071.
SEQ ID NO: 95 is the determined cDNA sequence of 13072.
SEQ ID NO: 96 is the determined cDNA sequence of 13073.
SEQ ID NO: 97 is the determined cDNA sequence of 13075.
10 SEQ ID NO: 98 is the determined cDNA sequence of 13078.
SEQ ID NO: 99 is the determined cDNA sequence of 13079.
SEQ ID NO: 100 is the determined cDNA sequence of 13081.
SEQ ID NO: 101 is the determined cDNA sequence of 13082.
SEQ ID NO: 102 is the determined cDNA sequence of 13092.
15 SEQ ID NO: 103 is the determined cDNA sequence of 13097.
SEQ ID NO: 104 is the determined cDNA sequence of 13101.
SEQ ID NO: 105 is the determined cDNA sequence of 13102.
SEQ ID NO: 106 is the determined cDNA sequence of 13119.
SEQ ID NO: 107 is the determined cDNA sequence of 13131.
20 SEQ ID NO: 108 is the determined cDNA sequence of 13133.
SEQ ID NO: 109 is the determined cDNA sequence of 13135.
SEQ ID NO: 110 is the determined cDNA sequence of 13139.
SEQ ID NO: 111 is the determined cDNA sequence of 13140.
SEQ ID NO: 112 is the determined cDNA sequence of 13146.
25 SEQ ID NO: 113 is the determined cDNA sequence of 13147.
SEQ ID NO: 114 is the determined cDNA sequence of 13148.
SEQ ID NO: 115 is the determined cDNA sequence of 13149.
SEQ ID NO: 116 is the determined cDNA sequence of 13151.
SEQ ID NO: 117 is the determined cDNA sequence of 13051
30 SEQ ID NO: 118 is the determined cDNA sequence of 13052
SEQ ID NO: 119 is the determined cDNA sequence of 13055
SEQ ID NO: 120 is the determined cDNA sequence of 13058

SEQ ID NO: 121 is the determined cDNA sequence of 13062
SEQ ID NO: 122 is the determined cDNA sequence of 13064
SEQ ID NO: 123 is the determined cDNA sequence of 13080
SEQ ID NO: 124 is the determined cDNA sequence of 13093
5 SEQ ID NO: 125 is the determined cDNA sequence of 13094
SEQ ID NO: 126 is the determined cDNA sequence of 13095
SEQ ID NO: 127 is the determined cDNA sequence of 13096
SEQ ID NO: 128 is the determined cDNA sequence of 13099
SEQ ID NO: 129 is the determined cDNA sequence of 13100
10 SEQ ID NO: 130 is the determined cDNA sequence of 13103
SEQ ID NO: 131 is the determined cDNA sequence of 13106
SEQ ID NO: 132 is the determined cDNA sequence of 13107
SEQ ID NO: 133 is the determined cDNA sequence of 13108
SEQ ID NO: 134 is the determined cDNA sequence of 13121
15 SEQ ID NO: 135 is the determined cDNA sequence of 13126
SEQ ID NO: 136 is the determined cDNA sequence of 13129
SEQ ID NO: 137 is the determined cDNA sequence of 13130
SEQ ID NO: 138 is the determined cDNA sequence of 13134
SEQ ID NO: 139 is the determined cDNA sequence of 13141
20 SEQ ID NO: 140 is the determined cDNA sequence of 13142
SEQ ID NO: 141 is the determined cDNA sequence of 14376
SEQ ID NO: 142 is the determined cDNA sequence of 14377
SEQ ID NO: 143 is the determined cDNA sequence of 14383
SEQ ID NO: 144 is the determined cDNA sequence of 14384
25 SEQ ID NO: 145 is the determined cDNA sequence of 14387
SEQ ID NO: 146 is the determined cDNA sequence of 14392
SEQ ID NO: 147 is the determined cDNA sequence of 14394
SEQ ID NO: 148 is the determined cDNA sequence of 14398
SEQ ID NO: 149 is the determined cDNA sequence of 14401
30 SEQ ID NO: 150 is the determined cDNA sequence of 14402
SEQ ID NO: 151 is the determined cDNA sequence of 14405
SEQ ID NO: 152 is the determined cDNA sequence of 14409
SEQ ID NO: 153 is the determined cDNA sequence of 14412

SEQ ID NO: 154 is the determined cDNA sequence of 14414
SEQ ID NO: 155 is the determined cDNA sequence of 14415
SEQ ID NO: 156 is the determined cDNA sequence of 14416
SEQ ID NO: 157 is the determined cDNA sequence of 14419
5 SEQ ID NO: 158 is the determined cDNA sequence of 14426
SEQ ID NO: 159 is the determined cDNA sequence of 14427
SEQ ID NO: 160 is the determined cDNA sequence of 14375
SEQ ID NO: 161 is the determined cDNA sequence of 14378
SEQ ID NO: 162 is the determined cDNA sequence of 14379
10 SEQ ID NO: 163 is the determined cDNA sequence of 14380
SEQ ID NO: 164 is the determined cDNA sequence of 14381
SEQ ID NO: 165 is the determined cDNA sequence of 14382
SEQ ID NO: 166 is the determined cDNA sequence of 14388
SEQ ID NO: 167 is the determined cDNA sequence of 14399
15 SEQ ID NO: 168 is the determined cDNA sequence of 14406
SEQ ID NO: 169 is the determined cDNA sequence of 14407
SEQ ID NO: 170 is the determined cDNA sequence of 14408
SEQ ID NO: 171 is the determined cDNA sequence of 14417
SEQ ID NO: 172 is the determined cDNA sequence of 14418
20 SEQ ID NO: 173 is the determined cDNA sequence of 14423
SEQ ID NO: 174 is the determined cDNA sequence of 14424
SEQ ID NO: 175 is the determined cDNA sequence of B726P-20
SEQ ID NO: 176 is the predicted amino acid sequence of B726P-20
SEQ ID NO: 177 is a PCR primer
25 SEQ ID NO: 178 is the determined cDNA sequence of B726P-74
SEQ ID NO: 179 is the predicted amino acid sequence of B726P-74
SEQ ID NO: 180 is the determined cDNA sequence of B726P-79
SEQ ID NO: 181 is the predicted amino acid sequence of B726P-79
SEQ ID NO: 182 is the determined cDNA sequence of 19439.1, showing
30 homology to the mammaglobin gene
SEQ ID NO: 183 is the determined cDNA sequence of 19407.1, showing
homology to the human keratin gene

SEQ ID NO: 184 is the determined cDNA sequence of 19428.1, showing homology to human chromosome 17 clone

SEQ ID NO: 185 is the determined cDNA sequence of B808P (19408), showing no significant homology to any known gene

5 SEQ ID NO: 186 is the determined cDNA sequence of 19460.1, showing no significant homology to any known gene

SEQ ID NO: 187 is the determined cDNA sequence of 19419.1, showing homology to Ig kappa light chain

10 SEQ ID NO: 188 is the determined cDNA sequence of 19411.1, showing homology to human alpha-1 collagen

SEQ ID NO: 189 is the determined cDNA sequence of 19420.1, showing homology to mus musculus proteinase-3

SEQ ID NO: 190 is the determined cDNA sequence of 19432.1, showing homology to human high motility group box

15 SEQ ID NO: 191 is the determined cDNA sequence of 19412.1, showing homology to the human plasminogen activator gene

SEQ ID NO: 192 is the determined cDNA sequence of 19415.1, showing homology to mitogen activated protein kinase

20 SEQ ID NO: 193 is the determined cDNA sequence of 19409.1, showing homology to the chondroitin sulfate proteoglycan protein

SEQ ID NO: 194 is the determined cDNA sequence of 19406.1, showing no significant homology to any known gene

SEQ ID NO: 195 is the determined cDNA sequence of 19421.1, showing homology to human fibronectin

25 SEQ ID NO: 196 is the determined cDNA sequence of 19426.1, showing homology to the retinoic acid receptor responder 3

SEQ ID NO: 197 is the determined cDNA sequence of 19425.1, showing homology to MyD88 mRNA

30 SEQ ID NO: 198 is the determined cDNA sequence of 19424.1, showing homology to peptide transporter (TAP-1) mRNA

SEQ ID NO: 199 is the determined cDNA sequence of 19429.1, showing no significant homology to any known gene

SEQ ID NO: 200 is the determined cDNA sequence of 19435.1, showing homology to human polymorphic epithelial mucin

SEQ ID NO: 201 is the determined cDNA sequence of B813P (19434.1), showing homology to human GATA-3 transcription factor

5 SEQ ID NO: 202 is the determined cDNA sequence of 19461.1, showing homology to the human AP-2 gene

SEQ ID NO: 203 is the determined cDNA sequence of 19450.1, showing homology to DNA binding regulatory factor

10 SEQ ID NO: 204 is the determined cDNA sequence of 19451.1, showing homology to Na/H exchange regulatory co-factor

SEQ ID NO: 205 is the determined cDNA sequence of 19462.1, showing no significant homology to any known gene

SEQ ID NO: 206 is the determined cDNA sequence of 19455.1, showing homology to human mRNA for histone HAS.Z

15 SEQ ID NO: 207 is the determined cDNA sequence of 19459.1, showing homology to PAC clone 179N16

SEQ ID NO: 208 is the determined cDNA sequence of 19464.1, showing no significant homology to any known gene

20 SEQ ID NO: 209 is the determined cDNA sequence of 19414.1, showing homology to lipophilin B

SEQ ID NO: 210 is the determined cDNA sequence of 19413.1, showing homology to chromosome 17 clone hRPK.209_J_20

SEQ ID NO: 211 is the determined cDNA sequence of 19416.1, showing no significant homology to any known gene

25 SEQ ID NO: 212 is the determined cDNA sequence of 19437.1, showing homology to human clone 24976 mRNA

SEQ ID NO: 213 is the determined cDNA sequence of 19449.1, showing homology to mouse DNA for PG-M core protein

30 SEQ ID NO: 214 is the determined cDNA sequence of 19446.1, showing no significant homology to any known gene

SEQ ID NO: 215 is the determined cDNA sequence of 19452.1, showing no significant homology to any known gene

SEQ ID NO: 216 is the determined cDNA sequence of 19483.1, showing no significant homology to any known gene

SEQ ID NO: 217 is the determined cDNA sequence of 19526.1, showing homology to human lipophilin C

5 SEQ ID NO: 218 is the determined cDNA sequence of 19484.1, showing homology to the secreted cement gland protein XAG-2

SEQ ID NO: 219 is the determined cDNA sequence of 19470.1, showing no significant homology to any known gene

10 SEQ ID NO: 220 is the determined cDNA sequence of 19469.1, showing homology to the human HLA-DM gene

SEQ ID NO: 221 is the determined cDNA sequence of 19482.1, showing homology to the human pS2 protein gene

SEQ ID NO: 222 is the determined cDNA sequence of B805P (19468.1), showing no significant homology to any known gene

15 SEQ ID NO: 223 is the determined cDNA sequence of 19467.1, showing homology to human thrombospondin mRNA

SEQ ID NO: 224 is the determined cDNA sequence of 19498.1, showing homology to the CDC2 gene involved in cell cycle control

20 SEQ ID NO: 225 is the determined cDNA sequence of 19506.1, showing homology to human cDNA for TREB protein

SEQ ID NO: 226 is the determined cDNA sequence of B806P (19505.1), showing no significant homology to any known gene

SEQ ID NO: 227 is the determined cDNA sequence of 19486.1, showing homology to type I epidermal keratin

25 SEQ ID NO: 228 is the determined cDNA sequence of 19510.1, showing homology to glucose transporter for glycoprotein

SEQ ID NO: 229 is the determined cDNA sequence of 19512.1, showing homology to the human lysyl hydroxylase gene

30 SEQ ID NO: 230 is the determined cDNA sequence of 19511.1, showing homology to human palmitoyl-protein thioesterase

SEQ ID NO: 231 is the determined cDNA sequence of 19508.1, showing homology to human alpha enolase

SEQ ID NO: 232 is the determined cDNA sequence of B807P (19509.1), showing no significant homology to any known gene

SEQ ID NO: 233 is the determined cDNA sequence of B809P (19520.1), showing homology to clone 102D24 on chromosome 11q13.31

5 SEQ ID NO: 234 is the determined cDNA sequence of 19507.1, showing homology to prosome beta-subunit

SEQ ID NO: 235 is the determined cDNA sequence of 19525.1, showing homology to human pro-urokinase precursor

10 SEQ ID NO: 236 is the determined cDNA sequence of 19513.1, showing no significant homology to any known gene

SEQ ID NO: 237 is the determined cDNA sequence of 19517.1, showing homology to human PAC 128M19 clone

SEQ ID NO: 238 is the determined cDNA sequence of 19564.1, showing homology to human cytochrome P450-IIB

15 SEQ ID NO: 239 is the determined cDNA sequence of 19553.1, showing homology to human GABA-A receptor pi subunit

SEQ ID NO: 240 is the determined cDNA sequence of B811P (19575.1), showing no significant homology to any known gene

20 SEQ ID NO: 241 is the determined cDNA sequence of B810P (19560.1), showing no significant homology to any known gene

SEQ ID NO: 242 is the determined cDNA sequence of 19588.1, showing homology to aortic carboxypeptidase-like protein

SEQ ID NO: 243 is the determined cDNA sequence of 19551.1, showing homology to human BCL-1 gene

25 SEQ ID NO: 244 is the determined cDNA sequence of 19567.1, showing homology to human proteasome-related mRNA

SEQ ID NO: 245 is the determined cDNA sequence of B803P (19583.1), showing no significant homology to any known gene

30 SEQ ID NO: 246 is the determined cDNA sequence of B812P (19587.1), showing no significant homology to any known gene

SEQ ID NO: 247 is the determined cDNA sequence of B802P (19392.2), showing homology to human chromosome 17

SEQ ID NO: 248 is the determined cDNA sequence of 19393.2, showing homology to human nicein B2 chain

SEQ ID NO: 249 is the determined cDNA sequence of 19398.2, human MHC class II DQ alpha mRNA

5 SEQ ID NO: 250 is the determined cDNA sequence of B804P (19399.2), showing homology to human Xp22 BAC GSHB-184P14

SEQ ID NO: 251 is the determined cDNA sequence of 19401.2, showing homology to human ikB kinase-b gene

10 SEQ ID NO: 252 is the determined cDNA sequence of 20266, showing no significant homology to any known gene

SEQ ID NO: 253 is the determined cDNA sequence of B826P (20270), showing no significant homology to any known gene

SEQ ID NO: 254 is the determined cDNA sequence of 20274, showing no significant homology to any known gene

15 SEQ ID NO: 255 is the determined cDNA sequence of 20276, showing no significant homology to any known gene

SEQ ID NO: 256 is the determined cDNA sequence of 20277, showing no significant homology to any known gene

20 SEQ ID NO: 257 is the determined cDNA sequence of B823P (20280), showing no significant homology to any known gene

SEQ ID NO: 258 is the determined cDNA sequence of B821P (20281), showing no significant homology to any known gene

SEQ ID NO: 259 is the determined cDNA sequence of B824P (20294), showing no significant homology to any known gene

25 SEQ ID NO: 260 is the determined cDNA sequence of 20303, showing no significant homology to any known gene

SEQ ID NO: 261 is the determined cDNA sequence of B820P (20310), showing no significant homology to any known gene

30 SEQ ID NO: 262 is the determined cDNA sequence of B825P (20336), showing no significant homology to any known gene

SEQ ID NO: 263 is the determined cDNA sequence of B827P (20341), showing no significant homology to any known gene

SEQ ID NO: 264 is the determined cDNA sequence of 20941, showing no significant homology to any known gene

SEQ ID NO: 265 is the determined cDNA sequence of 20954, showing no significant homology to any known gene

5 SEQ ID NO: 266 is the determined cDNA sequence of 20961, showing no significant homology to any known gene

SEQ ID NO: 267 is the determined cDNA sequence of 20965, showing no significant homology to any known gene

10 SEQ ID NO: 268 is the determined cDNA sequence of 20975, showing no significant homology to any known gene

SEQ ID NO: 269 is the determined cDNA sequence of 20261, showing homology to Human p120 catenin

SEQ ID NO: 270 is the determined cDNA sequence of B822P (20262), showing homology to Human membrane glycoprotein 4F2

15 SEQ ID NO: 271 is the determined cDNA sequence of 20265, showing homology to Human Na, K-ATPase Alpha 1

SEQ ID NO: 272 is the determined cDNA sequence of 20267, showing homology to Human heart HS 90, partial cds

20 SEQ ID NO: 273 is the determined cDNA sequence of 20268, showing homology to Human mRNA GPI-anchored protein p137

SEQ ID NO: 274 is the determined cDNA sequence of 20271, showing homology to Human cleavage stimulation factor 77 kDa subunit

SEQ ID NO: 275 is the determined cDNA sequence of 20272, showing homology to Human p190-B

25 SEQ ID NO: 276 is the determined cDNA sequence of 20273, showing homology to Human ribophorin

SEQ ID NO: 277 is the determined cDNA sequence of 20278, showing homology to Human ornithine amino transferase

30 SEQ ID NO: 278 is the determined cDNA sequence of 20279, showing homology to Human S-adenosylmethionine synthetase

SEQ ID NO: 279 is the determined cDNA sequence of 20293, showing homology to Human x inactivation transcript

SEQ ID NO: 280 is the determined cDNA sequence of 20300, showing homology to Human cytochrome p450

SEQ ID NO: 281 is the determined cDNA sequence of 20305, showing homology to Human elongation factor-1 alpha

5 SEQ ID NO: 282 is the determined cDNA sequence of 20306, showing homology to Human epithelial ets protein

SEQ ID NO: 283 is the determined cDNA sequence of 20307, showing homology to Human signal transducer mRNA

10 SEQ ID NO: 284 is the determined cDNA sequence of 20313, showing homology to Human GABA-A receptor pi subunit mRNA

SEQ ID NO: 285 is the determined cDNA sequence of 20317, showing homology to Human tyrosine phosphatase

SEQ ID NO: 286 is the determined cDNA sequence of 20318, showing homology to Human cathepsine B proteinase

15 SEQ ID NO: 287 is the determined cDNA sequence of 20320, showing homology to Human 2-phosphopyruvate-hydratase-alpha-enolase

SEQ ID NO: 288 is the determined cDNA sequence of 20321, showing homology to Human E-cadherin

20 SEQ ID NO: 289 is the determined cDNA sequence of 20322, showing homology to Human hsp86

SEQ ID NO: 290 is the determined cDNA sequence of B828P (20326), showing homology to Human x inactivation transcript

SEQ ID NO: 291 is the determined cDNA sequence of 20333, showing homology to Human chromatin regulator, SMARCA5

25 SEQ ID NO: 292 is the determined cDNA sequence of 20335, showing homology to Human sphingolipid activator protein 1

SEQ ID NO: 293 is the determined cDNA sequence of 20337, showing homology to Human hepatocyte growth factor activator inhibitor type 2

30 SEQ ID NO: 294 is the determined cDNA sequence of 20338, showing homology to Human cell adhesion molecule CD44

SEQ ID NO: 295 is the determined cDNA sequence of 20340, showing homology to Human nuclear factor (erythroid-derived)-like 1

SEQ ID NO: 296 is the determined cDNA sequence of 20938, showing homology to Human vinculin mRNA

SEQ ID NO: 297 is the determined cDNA sequence of 20939, showing homology to Human elongation factor EF-1-alpha

5 SEQ ID NO: 298 is the determined cDNA sequence of 20940, showing homology to Human nestin gene

SEQ ID NO: 299 is the determined cDNA sequence of 20942, showing homology to Human pancreatic ribonuclease

10 SEQ ID NO: 300 is the determined cDNA sequence of 20943, showing homology to Human transcobalamin I

SEQ ID NO: 301 is the determined cDNA sequence of 20944, showing homology to Human beta-tubulin

SEQ ID NO: 302 is the determined cDNA sequence of 20946, showing homology to Human HS1 protein

15 SEQ ID NO: 303 is the determined cDNA sequence of 20947, showing homology to Human cathepsin B

SEQ ID NO: 304 is the determined cDNA sequence of 20948, showing homology to Human testis enhanced gene transcript

20 SEQ ID NO: 305 is the determined cDNA sequence of 20949, showing homology to Human elongation factor EF-1-alpha

SEQ ID NO: 306 is the determined cDNA sequence of 20950, showing homology to Human ADP-ribosylation factor 3

SEQ ID NO: 307 is the determined cDNA sequence of 20951, showing homology to Human IFP53 or WRS for tryptophanyl-tRNA synthetase

25 SEQ ID NO: 308 is the determined cDNA sequence of 20952, showing homology to Human cyclin-dependent protein kinase

SEQ ID NO: 309 is the determined cDNA sequence of 20957, showing homology to Human alpha-tubulin isoform 1

30 SEQ ID NO: 310 is the determined cDNA sequence of 20959, showing homology to Human tyrosine phosphatase-61bp deletion

SEQ ID NO: 311 is the determined cDNA sequence of 20966, showing homology to Human tyrosine phosphatase

SEQ ID NO: 312 is the determined cDNA sequence of B830P (20976), showing homology to Human nuclear factor NF 45

SEQ ID NO: 313 is the determined cDNA sequence of B829P (20977), showing homology to Human delta-6 fatty acid desaturase

5 SEQ ID NO: 314 is the determined cDNA sequence of 20978, showing homology to Human nuclear aconitase

SEQ ID NO: 315 is the determined cDNA sequence of clone 23176.

SEQ ID NO: 316 is the determined cDNA sequence of clone 23140.

SEQ ID NO: 317 is the determined cDNA sequence of clone 23166.

10 SEQ ID NO: 318 is the determined cDNA sequence of clone 23167.

SEQ ID NO: 319 is the determined cDNA sequence of clone 23177.

SEQ ID NO: 320 is the determined cDNA sequence of clone 23217.

SEQ ID NO: 321 is the determined cDNA sequence of clone 23169.

SEQ ID NO: 322 is the determined cDNA sequence of clone 23160.

15 SEQ ID NO: 323 is the determined cDNA sequence of clone 23182.

SEQ ID NO: 324 is the determined cDNA sequence of clone 23232.

SEQ ID NO: 325 is the determined cDNA sequence of clone 23203.

SEQ ID NO: 326 is the determined cDNA sequence of clone 23198.

SEQ ID NO: 327 is the determined cDNA sequence of clone 23224.

20 SEQ ID NO: 328 is the determined cDNA sequence of clone 23142.

SEQ ID NO: 329 is the determined cDNA sequence of clone 23138.

SEQ ID NO: 330 is the determined cDNA sequence of clone 23147.

SEQ ID NO: 331 is the determined cDNA sequence of clone 23148.

SEQ ID NO: 332 is the determined cDNA sequence of clone 23149.

25 SEQ ID NO: 333 is the determined cDNA sequence of clone 23172.

SEQ ID NO: 334 is the determined cDNA sequence of clone 23158.

SEQ ID NO: 335 is the determined cDNA sequence of clone 23156.

SEQ ID NO: 336 is the determined cDNA sequence of clone 23221.

SEQ ID NO: 337 is the determined cDNA sequence of clone 23223.

30 SEQ ID NO: 338 is the determined cDNA sequence of clone 23155.

SEQ ID NO: 339 is the determined cDNA sequence of clone 23225.

SEQ ID NO: 340 is the determined cDNA sequence of clone 23226.

SEQ ID NO: 341 is the determined cDNA sequence of clone 23228.

SEQ ID NO: 342 is the determined cDNA sequence of clone 23229.
SEQ ID NO: 343 is the determined cDNA sequence of clone 23231.
SEQ ID NO: 344 is the determined cDNA sequence of clone 23154.
SEQ ID NO: 345 is the determined cDNA sequence of clone 23157.
5 SEQ ID NO: 346 is the determined cDNA sequence of clone 23153.
SEQ ID NO: 347 is the determined cDNA sequence of clone 23159.
SEQ ID NO: 348 is the determined cDNA sequence of clone 23152.
SEQ ID NO: 349 is the determined cDNA sequence of clone 23161.
SEQ ID NO: 350 is the determined cDNA sequence of clone 23162.
10 SEQ ID NO: 351 is the determined cDNA sequence of clone 23163.
SEQ ID NO: 352 is the determined cDNA sequence of clone 23164.
SEQ ID NO: 353 is the determined cDNA sequence of clone 23165.
SEQ ID NO: 354 is the determined cDNA sequence of clone 23151.
SEQ ID NO: 355 is the determined cDNA sequence of clone 23150.
15 SEQ ID NO: 356 is the determined cDNA sequence of clone 23168.
SEQ ID NO: 357 is the determined cDNA sequence of clone 23146.
SEQ ID NO: 358 is the determined cDNA sequence of clone 23170.
SEQ ID NO: 359 is the determined cDNA sequence of clone 23171.
SEQ ID NO: 360 is the determined cDNA sequence of clone 23145.
20 SEQ ID NO: 361 is the determined cDNA sequence of clone 23174.
SEQ ID NO: 362 is the determined cDNA sequence of clone 23175.
SEQ ID NO: 363 is the determined cDNA sequence of clone 23144.
SEQ ID NO: 364 is the determined cDNA sequence of clone 23178.
SEQ ID NO: 365 is the determined cDNA sequence of clone 23179.
25 SEQ ID NO: 366 is the determined cDNA sequence of clone 23180.
SEQ ID NO: 367 is the determined cDNA sequence of clone 23181.
SEQ ID NO: 368 is the determined cDNA sequence of clone 23143.
SEQ ID NO: 369 is the determined cDNA sequence of clone 23183.
SEQ ID NO: 370 is the determined cDNA sequence of clone 23184.
30 SEQ ID NO: 371 is the determined cDNA sequence of clone 23185.
SEQ ID NO: 372 is the determined cDNA sequence of clone 23186.
SEQ ID NO: 373 is the determined cDNA sequence of clone 23187.
SEQ ID NO: 374 is the determined cDNA sequence of clone 23190.

SEQ ID NO: 375 is the determined cDNA sequence of clone 23189.
SEQ ID NO: 376 is the determined cDNA sequence of clone 23202.
SEQ ID NO: 378 is the determined cDNA sequence of clone 23191.
SEQ ID NO: 379 is the determined cDNA sequence of clone 23188.
5 SEQ ID NO: 380 is the determined cDNA sequence of clone 23194.
SEQ ID NO: 381 is the determined cDNA sequence of clone 23196.
SEQ ID NO: 382 is the determined cDNA sequence of clone 23195.
SEQ ID NO: 383 is the determined cDNA sequence of clone 23193.
SEQ ID NO: 384 is the determined cDNA sequence of clone 23199.
10 SEQ ID NO: 385 is the determined cDNA sequence of clone 23200.
SEQ ID NO: 386 is the determined cDNA sequence of clone 23192.
SEQ ID NO: 387 is the determined cDNA sequence of clone 23201.
SEQ ID NO: 388 is the determined cDNA sequence of clone 23141.
SEQ ID NO: 389 is the determined cDNA sequence of clone 23139.
15 SEQ ID NO: 390 is the determined cDNA sequence of clone 23204.
SEQ ID NO: 391 is the determined cDNA sequence of clone 23205.
SEQ ID NO: 392 is the determined cDNA sequence of clone 23206.
SEQ ID NO: 393 is the determined cDNA sequence of clone 23207.
SEQ ID NO: 394 is the determined cDNA sequence of clone 23208.
20 SEQ ID NO: 395 is the determined cDNA sequence of clone 23209.
SEQ ID NO: 396 is the determined cDNA sequence of clone 23210.
SEQ ID NO: 397 is the determined cDNA sequence of clone 23211.
SEQ ID NO: 398 is the determined cDNA sequence of clone 23212.
SEQ ID NO: 399 is the determined cDNA sequence of clone 23214.
25 SEQ ID NO: 400 is the determined cDNA sequence of clone 23215.
SEQ ID NO: 401 is the determined cDNA sequence of clone 23216.
SEQ ID NO: 402 is the determined cDNA sequence of clone 23137.
SEQ ID NO: 403 is the determined cDNA sequence of clone 23218.
SEQ ID NO: 404 is the determined cDNA sequence of clone 23220.
30 SEQ ID NO: 405 is the determined cDNA sequence of clone 19462.
SEQ ID NO: 406 is the determined cDNA sequence of clone 19430.
SEQ ID NO: 407 is the determined cDNA sequence of clone 19407.
SEQ ID NO: 408 is the determined cDNA sequence of clone 19448.

SEQ ID NO: 409 is the determined cDNA sequence of clone 19447.
SEQ ID NO: 410 is the determined cDNA sequence of clone 19426.
SEQ ID NO: 411 is the determined cDNA sequence of clone 19441.
SEQ ID NO: 412 is the determined cDNA sequence of clone 19454.
5 SEQ ID NO: 413 is the determined cDNA sequence of clone 19463.
SEQ ID NO: 414 is the determined cDNA sequence of clone 19419.
SEQ ID NO: 415 is the determined cDNA sequence of clone 19434.
SEQ ID NO: 416 is the determined extended cDNA sequence of B820P.
SEQ ID NO: 417 is the determined extended cDNA sequence of B821P.
10 SEQ ID NO: 418 is the determined extended cDNA sequence of B822P.
SEQ ID NO: 419 is the determined extended cDNA sequence of B823P.
SEQ ID NO: 420 is the determined extended cDNA sequence of B824P.
SEQ ID NO: 421 is the determined extended cDNA sequence of B825P.
SEQ ID NO: 422 is the determined extended cDNA sequence of B826P.
15 SEQ ID NO: 423 is the determined extended cDNA sequence of B827P.
SEQ ID NO: 424 is the determined extended cDNA sequence of B828P.
SEQ ID NO: 425 is the determined extended cDNA sequence of B829P.
SEQ ID NO: 426 is the determined extended cDNA sequence of B830P.
SEQ ID NO: 427 is the determined cDNA sequence of clone 266B4.
20 SEQ ID NO: 428 is the determined cDNA sequence of clone 22892.
SEQ ID NO: 429 is the determined cDNA sequence of clone 266G3.
SEQ ID NO: 430 is the determined cDNA sequence of clone 22890.
SEQ ID NO: 431 is the determined cDNA sequence of clone 264B4.
SEQ ID NO: 432 is the determined cDNA sequence of clone 22883.
25 SEQ ID NO: 433 is the determined cDNA sequence of clone 22882.
SEQ ID NO: 434 is the determined cDNA sequence of clone 22880.
SEQ ID NO: 435 is the determined cDNA sequence of clone 263G1.
SEQ ID NO: 436 is the determined cDNA sequence of clone 263G6.
SEQ ID NO: 437 is the determined cDNA sequence of clone 262B2.
30 SEQ ID NO: 438 is the determined cDNA sequence of clone 262B6.
SEQ ID NO: 439 is the determined cDNA sequence of clone 22869.
SEQ ID NO: 440 is the determined cDNA sequence of clone 21374.
SEQ ID NO: 441 is the determined cDNA sequence of clone 21362.

SEQ ID NO: 442 is the determined cDNA sequence of clone 21349.
SEQ ID NO: 443 is the determined cDNA sequence of clone 21309.
SEQ ID NO: 444 is the determined cDNA sequence of clone 21097.
SEQ ID NO: 445 is the determined cDNA sequence of clone 21096.
5 SEQ ID NO: 446 is the determined cDNA sequence of clone 21094.
SEQ ID NO: 447 is the determined cDNA sequence of clone 21093.
SEQ ID NO: 448 is the determined cDNA sequence of clone 21091.
SEQ ID NO: 449 is the determined cDNA sequence of clone 21089.
SEQ ID NO: 450 is the determined cDNA sequence of clone 21087.
10 SEQ ID NO: 451 is the determined cDNA sequence of clone 21085.
SEQ ID NO: 452 is the determined cDNA sequence of clone 21084.
SEQ ID NO: 453 is a first partial cDNA sequence of clone 2BT1-40.
SEQ ID NO: 454 is a second partial cDNA sequence of clone 2BT1-40.
SEQ ID NO: 455 is the determined cDNA sequence of clone 21063.
15 SEQ ID NO: 456 is the determined cDNA sequence of clone 21062.
SEQ ID NO: 457 is the determined cDNA sequence of clone 21060.
SEQ ID NO: 458 is the determined cDNA sequence of clone 21053.
SEQ ID NO: 459 is the determined cDNA sequence of clone 21050.
SEQ ID NO: 460 is the determined cDNA sequence of clone 21036.
20 SEQ ID NO: 461 is the determined cDNA sequence of clone 21037.
SEQ ID NO: 462 is the determined cDNA sequence of clone 21048.
SEQ ID NO: 463 is a consensus DNA sequence of B726P (referred to as
B726P-spliced_seq_B726P).
SEQ ID NO: 464 is the determined cDNA sequence of a second splice
25 form of B726P (referred to as 27490.seq_B726P).
SEQ ID NO: 465 is the determined cDNA sequence of a third splice
form of B726P (referred to as 27068.seq_B726P).
SEQ ID NO: 466 is the determined cDNA sequence of a second splice
form of B726P (referred to as 23113.seq_B726P).
30 SEQ ID NO: 467 is the determined cDNA sequence of a second splice
form of B726P (referred to as 23103.seq_B726P).
SEQ ID NO: 468 is the determined cDNA sequence of a second splice
form of B726P (referred to as 19310.seq_B726P).

SEQ ID NO: 469 is the predicted amino acid sequence encoded by the upstream ORF of SEQ ID NO: 463.

SEQ ID NO: 470 is the predicted amino acid sequence encoded by SEQ ID NO: 464.

5 SEQ ID NO: 471 is the predicted amino acid sequence encoded by SEQ ID NO: 465.

SEQ ID NO: 472 is the predicted amino acid sequence encoded by SEQ ID NO: 466.

10 SEQ ID NO: 473 is the predicted amino acid sequence encoded by SEQ ID NO: 467.

SEQ ID NO: 474 is the determined cDNA sequence for an alternative splice form of B726P.

SEQ ID NO: 475 is the amino acid sequence encoded by SEQ ID NO: 474.

15 SEQ ID NO: 476 is the isolated cDNA sequence of B720P.

SEQ ID NO: 477 is the cDNA sequence of a known keratin gene.

SEQ ID NO: 478 is the amino acid sequence encoded by SEQ ID NO: 477.

SEQ ID NO: 479 is the determined cDNA sequence for clone 19465.

20 SEQ ID NO: 480 and 481 are PCR primers.

SEQ ID NO: 482 is the cDNA sequence for the expressed downstream ORF of B726P.

SEQ ID NO: 483 is the amino acid sequence for the expressed recombinant downstream ORF of B726P.

25 SEQ ID NO: 484 is the determined full-length cDNA sequence for B720P.

SEQ ID NO: 485 is the amino acid sequence encoded by SEQ ID NO: 484.

30 SEQ ID NO: 486 is the determined cDNA sequence of a truncated form of B720P, referred to as B720P-tr.

SEQ ID NO: 487 is the amino acid sequence of B720P-tr.

SEQ ID NO: 488 is the amino acid sequence of a naturally processed epitope of B726P recognized by B726P-specific CTL.

SEQ ID NO: 489 is a DNA sequence encoding the B726P epitope set forth in SEQ ID NO: 488.

SEQ ID NO: 490 is a DNA sequence encoding a fusion protein wherein mammaglobin is fused to a B726P combined upstream and downstream open reading
5 frame (ORF) (the amino acid sequence of the B726P combined ORF is disclosed herein by SEQ ID NO: 475 which is encoded by the DNA sequence of SEQ ID NO: 474).

SEQ ID NO: 491 is a DNA sequence encoding a fusion protein wherein mammaglobin is fused to a B726P upstream ORF (the amino acid sequence of the B726P upstream ORF is disclosed herein by SEQ ID NO: 469 which is encoded by the
10 DNA sequence of SEQ ID NO: 463).

SEQ ID NO: 492 is a DNA sequence encoding a fusion protein wherein mammaglobin is fused to a B726P downstream ORF (the amino acid sequence of the B726P downstream ORF is disclosed herein by SEQ ID NO: 176 which is encoded by the DNA sequence of SEQ ID NO: 175).

15 SEQ ID NO: 493 is the amino acid sequence encoded by the DNA sequence of SEQ ID NO: 490.

SEQ ID NO: 494 is the amino acid sequence encoded by the DNA sequence of SEQ ID NO: 491.

SEQ ID NO: 495 is the amino acid sequence encoded by the DNA
20 sequence of SEQ ID NO: 492.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of cancer, such as breast cancer. Certain illustrative compositions described
25 herein include breast tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). A "breast tumor protein," as the term is used herein, refers generally to a protein that is expressed in breast tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal
30 tissue, as determined using a representative assay provided herein. Certain breast tumor

proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with breast cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set forth in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489, illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NO: 176, 179, 181, 469-473, 475, 485, 487 and 488, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human breast cancer.

POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and
5 mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous
10 sequence that encodes a breast tumor protein or a portion thereof) or may comprise a variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The
15 effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. The term “variants” also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be “identical” if the sequence of nucleotides or amino acids in the
20 two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A “comparison window” as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence
25 may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several
30 alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.

In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenesis pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

10 Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these
15 algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0
20 algorithms, which are described in Altschul *et al.* (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for
25 Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the
30 cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or

more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix
5 (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the
10 comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to
15 yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for
20 example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be
25 appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of
30 sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at

least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear

minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention.

- 5 Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

10 PROBES AND PRIMERS

- In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the
- 15 same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

- 20 The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

- 25 Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow
- 30 a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also

in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477 479, 484, 486 and 489, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCRTM technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using any of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto,

CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as breast tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, a breast tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then be assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques,

amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target
5 sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia *et al.*, *Nucl. Acids Res.* 16:8186, 1988), which uses restriction enzymes to generate a fragment
10 in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of
15 amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer,
20 which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom *et al.*, *PCR Methods Applic.* 1:111-19, 1991) and walking PCR (Parker *et al.*, *Nucl. Acids. Res.* 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

25 In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences
30 may also be obtained by analysis of genomic fragments.

POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct
5 expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous
10 in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring
15 sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For
20 example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

25 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be
30 engineered to contain a cleavage site located between the polypeptide-encoding

sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. *et al.* (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; 5 insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an 10 expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. 15 For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSFORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains 20 multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which 25 direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of β -galactosidase so that a 30 hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.)

may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J.* 3:1671-1680; Broglie, R. *et al.* (1984) *Science* 224:838-843; and Winter, J. *et al.* (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda*

cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. *et al.* (1994) *Proc. Natl. Acad. Sci.* 91 :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression
5 vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition,
10 transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the
15 polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct
20 reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. *et al.* (1994) *Results Probl. Cell Differ.* 20:125-162).

25 In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be
30 used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and

characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a
5 polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer
10 resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine
15 kinase (Wigler, M. *et al.* (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. *et al.* (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. *et al.* (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which
20 confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. *et al.* (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in
25 place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific
30 vector system (Rhodes, C. A. *et al.* (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the
5 absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired
10 polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

15 A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal
20 antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul, Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med.* 158:1211-1216).

25 A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions
30 thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA

probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents
5 as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood
10 by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate
15 purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker
20 sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues
25 facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. *et al.* (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. *et al.* (1993; *DNA Cell Biol.* 12:441-453).

30 In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using

solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically
5 synthesized separately and combined using chemical methods to produce the full length molecule.

SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific
10 mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific
15 oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the
20 properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the antigenicity of a polypeptide
25 vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of
30 the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily
5 commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of
10 a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-
15 bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

20 The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence
25 may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kubly, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis
30 procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule

relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent
5 process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of
10 the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification
15 methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture
20 along with a DNA polymerase (e.g., *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the
25 target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to
30 as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated

herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR™, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[α-thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the

products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

5 Still other amplification methods described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by
10 labeling with a capture moiety (*e.g.*, biotin) and/or a detector moiety (*e.g.*, enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

15 Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh *et al.*, 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation
20 of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded
25 DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate
30 target-specific sequences.

Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template
5 for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase
10 promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter
15 sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or
20 RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This
25 scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide",
30 thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by

reference in its entirety), may also be used in the amplification of DNA sequences of the present invention.

BIOLOGICAL FUNCTIONAL EQUIVALENTS

Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids				Codons				
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are:

isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 \pm 1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of
5 flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

10 IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety of well known approaches, several of which are outlined below for the purpose of illustration.

15 1. ADENOVIRUS

One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to express a
20 polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear,
25 double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement

has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5'-tripartite leader (TPL) sequence which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package

approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may

be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, *e.g.*, 10^9 - 10^{11} plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch *et al.*, 1963; Top *et al.*, 1971), demonstrating their safety and therapeutic potential as *in vivo* gene transfer vectors.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero *et al.*, 1991; Gomez-Foix *et al.*, 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet *et al.*, 1990; Rich *et al.*, 1993). Studies in administering recombinant adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993),

peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

2. RETROVIRUSES

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

- 5 A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection
10 of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

3. ADENO-ASSOCIATED VIRUSES

- AAV (Ridgeway, 1988; Hermonat and Muzycska, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies
15 are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of
20 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

- The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replications, whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped
25 hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins,

and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector. One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with foreign genetic material. The hepatotropism and persistence (integration) were particularly attractive properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenicol acetyltransferase (CAT) gene into duck hepatitis B

virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days
5 after transfection (Chang *et al.*, 1991).

5. NON-VIRAL VECTORS

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for
10 transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be
15 positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be
20 stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

25 In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell membrane. This is particularly applicable for transfer *in vitro* but
30 it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected

polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes.

- 5 It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity
10 allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

- 15 Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e.* *ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present
20 invention.

ANTISENSE OLIGONUCLEOTIDES

- The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the
25 route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic

antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA_A receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore, in exemplary embodiments, the invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T_m , binding

energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or
5 near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

10 The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense
15 oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

RIBOZYMES

20 Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a
25 large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence
30 ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech *et al.*, 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence
5 specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes
10 H-ras, c-fos and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general,
15 enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to
20 cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many
25 technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of
30 target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target

RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action of a ribozyme is greater than that of
5 an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* (1992). Examples of hairpin motifs are described by Hampel
10 *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel *et al.* (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis δ virus motif is described by Perrotta and Been (1992); an example of the RNaseP motif is described by Guerrier-Takada *et al.* (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins,
15 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or
20 surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired
25 target, such as one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific cells.

30 Small enzymatic nucleic acid motifs (*e.g.*, of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of

these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells from eukaryotic promoters (*e.g.*, Scanlon *et al.*, 1991; Kashani-Sabet *et al.*, 1992; Dropulic *et al.*, 1992; Weerasinghe *et al.*, 1991; Ojwang *et al.*, 1992; 5 Chen *et al.*, 1992; Sarver *et al.*, 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No. WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa *et al.*, 10 1992; Taira *et al.*, 1991; and Ventura *et al.*, 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, aerosol inhalation, infusion pump or stent, with or 15 without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific 20 examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger *et al.*, 1989) to assess whether the ribozyme sequences fold into the appropriate secondary structure. Those ribozymes with unfavorable 25 intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to 30 anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described

in Usman *et al.* (1987) and in Scaringe *et al.* (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an
5 active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-o-methyl, 2'-H (for a review see *e.g.*, Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

10 Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al.*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur.
15 Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

20 Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable
25 nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular,
30 subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions

of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber *et al.*, 1993; Zhou *et al.*, 1990). Ribozymes expressed from such promoters can function in mammalian cells (*e.g.* Kashani-Saber *et al.*, 1992; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Yu *et al.*, 1993; L'Huillier *et al.*, 1992; Lisiewicz *et al.*, 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational

therapies (*e.g.*, multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes are well known in the art, and include detection of the presence of mRNA
5 associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

PEPTIDE NUCLEIC ACIDS

In certain embodiments, the inventors contemplate the use of peptide
10 nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA
15 or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-
20 specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Neilsen, 1996). This chemistry has three important consequences:
25 firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used
30 (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton *et al.*, 1995; Haaima *et al.*, 1996; Stetsenko *et al.*, 1996; Petersen *et al.*, 1995; Ulmann *et al.*, 1996; Koch *et al.*, 1995; Orum *et al.*, 1995; Footer *et al.*, 1996; Griffith *et al.*, 1995; Kremisky *et al.*, 1996; Pardridge *et al.*, 1995; Boffa *et al.*, 1995; Landsdorp *et al.*, 1996; Gambacorti-Passerini *et al.*, 1996; Armitage *et al.*, 1997; Seeger *et al.*, 1997; Ruskowski *et al.*, 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs

recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3' to 5' polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

5 Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature (T_m) and reduces the dependence of T_m on the concentration of mono- or divalent cations
10 (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced
15 recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.* have shown that support-bound PNAs can be used to detect hybridization events (Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing
20 the sequence specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a single mismatch within a 16 bp PNA-DNA duplex can reduce the T_m by
25 up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

High-affinity binding provides clear advantages for molecular
30 recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends

telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers, and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

Findings by Allfrey and colleagues suggest that strand invasion will occur spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to inhibit transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and Good and Nielsen (1997). Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen *et al.*, 1991), antisense inhibition (Hanvey *et al.*, 1992), mutational analysis (Orum *et al.*, 1993), enhancers of transcription (Mollegaard *et al.*, 1994), nucleic acid purification (Orum *et al.*, 1995), isolation of transcriptionally active genes (Boffa *et al.*, 1995), blocking of transcription factor binding (Vickers *et al.*, 1995), genome cleavage (Veselkov *et al.*, 1996), biosensors (Wang *et al.*, 1996), *in situ* hybridization (Thisted *et al.*, 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

POLYPEPTIDE COMPOSITIONS

The present invention, in other aspects, provides polypeptide compositions. Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species.

5 Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid

10 sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the amino acid sequence disclosed in SEQ ID NO: 176, 179, 181, 469-473, 475, 485, 487

15 and 488, or to active fragments, or to variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are immunologically reactive with one or more polypeptides encoded by one or

20 more contiguous nucleic acid sequences contained in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477 479, 484, 486 and 489, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency. Particularly illustrative polypeptides include the amino acid sequence disclosed in SEQ ID NO: 176,

25 179, 181, 469-473, 475, 485, 487 and 488.

As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as

30 described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a breast tumor protein or a variant thereof, as described herein. As noted above, a "breast tumor protein" is a protein that is expressed by breast tumor cells. Proteins that are breast tumor proteins also react
5 detectably within an immunoassay (such as an ELISA) with antisera from a patient with breast cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

10 An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a breast tumor protein or a variant thereof. Certain preferred immunogenic
15 portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known
20 techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an
25 ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native breast tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell
30 reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such

5 screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

As noted above, a composition may comprise a variant of a native breast tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native breast tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

25 Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively

charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine.

- 5 Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer.
- 10 Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

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Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange

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resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See Merrifield, J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase.

This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide
5 folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second
10 polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea *et al.*, *Gene* 40:39-46, 1985; Murphy *et al.*,
15 *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

20 The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the
25 second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute *et al.* *New Engl. J. Med.*, 336:86-91, 1997).
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Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred
5 embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells.
10 Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is
15 derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This
20 property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-
25 terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is
30 isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at

least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

In order to improve the antigenicity and/or immunogenicity of breast
5 tumor proteins according to the present invention, fusion proteins comprising antigenic and/or immunogenic portions of two or more breast tumor proteins may be prepared. Exemplary breast tumor fusion proteins may be prepared through conventional recombinant DNA methodology by combining a DNA sequence encoding
10 mammaglobin with a DNA sequence encoding either (1) the combined B726P upstream and downstream ORFs (SEQ ID NO: 490), (2) the upstream B726P ORF (SEQ ID NO: 491), and/or (3) the downstream B726P ORF (SEQ ID NO: 492). *See, e.g.,* Ausubel, F.M. *et al.*, "Short Protocols in Molecular Biology" (4th ed. 1999); incorporated herein by reference in its entirety). Exemplary fusion proteins are disclosed herein by SEQ ID NO: 493 (mammaglobin-combined B726P ORF), SEQ ID NO: 494 (mammaglobin-
15 upstream B726P ORF), and SEQ ID NO: 495 (mammaglobin-downstream B726P ORF). The DNA sequence encoding mammaglobin is disclosed herein by nucleotides 1-279 of SEQ ID NOs: 490-492 and the corresponding mammaglobin amino acid sequence is disclosed herein as amino acids 1-93 of SEQ ID NOs: 493-495. *See, also,* U.S. Patent No. 5,668,267; U.S. Patent No. 5,922,836; U.S. Patent No. 5,855,889; U.S.
20 Patent No. 5,968,754; and U.S. Patent No. 6,004,756, each of which U.S. Patent is incorporated by reference herein in its entirety.

In addition to the exemplary fusion proteins prepared by the fusion of a full-length mammaglobin coding region with various B726P coding regions, the present
25 invention further provides fusion proteins comprising immunogenic portions of 9 or more contiguous amino acids from either or both of mammaglobin and B726P. More preferably, immunogenic portions may be 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more contiguous amino acids from either or both of mammaglobin and/or B726P. Alternatively, immunogenic portions may be at least 25, 30, 35, 40, 45, 50, 75, 100,
30 250, 500, or 1095 contiguous amino acids from either or both of mammaglobin and/or

B726P and may also include any integral number of amino acids between 20 and 1095 contiguous amino acids from either or both of mammaglobin and/or B726P.

Representative immunogenic portions of mammaglobin are disclosed in
co-

- 5 pending U.S. Patent Application 60/136,528. Exemplary immunogenic portions include the following mammaglobin peptide sequences: IDELKECFLNQTDETLSNVE (amino acids 59-78 of SEQ ID NO: 493); TTNAIDELKECFLNQ (amino acids 55-69 of SEQ ID NO: 493); SQHCYAGSGCPLEENVISKTI (amino acids 13-33 of SEQ ID NO: 493); EYKELLQEFIDDNATTNAID (amino acids 41-60 of SEQ ID NO: 493),
10 and/or KLLMVLMLA (amino acids 2-10 of SEQ ID NO: 493). Other preferred epitopes comprise a glycosylation site of mammaglobin. Such epitopes are particularly useful for the generation of antibodies that specifically bind to glycosylated mammaglobin. Two such sites are the N-linked glycosylation sites asparagine (Asp)-53 (QEFIDDNATTNAI; amino acids 47-59 of SEQ ID NO: 493) and Asp-68
15 (LKECFLNQDDETL; amino acids 62-74 of SEQ ID NO: 493).

- The present invention also contemplates that a wide variety of immunogenic portions from the B726P combined, B726P upstream, and/or B726P downstream amino acid sequences may find use in mammaglobin-B726P fusion proteins. For example, a particularly suitable mammaglobin-B726P fusion protein may
20 be prepared by fusing mammaglobin to a downstream B726P epitope recognized by B726P-specific CTL clones, described herein in Example 4, which epitope is included within the N-terminal end of the downstream region of B726P (*i.e.* amino acids 1-129 of SEQ ID NO: 176).

- It will be apparent to those of skill in the art that the precise amino acid
25 sequence and primary sequence arrangement of the mammaglobin and/or B726P portions of the fusion proteins may be varied without deviating from the scope of the present invention. For example, conservative amino acids substitutions within either or both of the mammaglobin or B726P portions may be made, for example, to achieve fusion proteins having improved properties such as increased protein stability and/or
30 immunogenicity. In addition, the present invention contemplates that the mammaglobin

portion may be fused to either the N-terminus or C-terminus of the B726P portion to achieve fusion proteins that have the desired antigenic and/or immunogenic properties.

Fusion proteins according to the present invention, as exemplified by the mammaglobin-B726P fusion proteins disclosed herein by this Example, will find use as cancer vaccines, reagents for antibody therapeutics, and/or in various diagnostic assays. It is expected that these fusion proteins will have improved antigenic and/or immunogenic properties as compared to either the mammaglobin and/or B726P proteins alone.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a breast tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a breast tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a breast tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as breast cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a breast tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a

cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of
5 ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an
10 antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into
15 suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short
20 polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified
25 from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve
30 the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may

be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells
5 and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture
10 supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable
15 vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

20 Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested
25 by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides
30 include ^{90}Y , ^{123}I , ^{125}I , ^{131}I , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers

include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a
5 suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group
10 containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an
15 agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described
20 in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*

Where a therapeutic agent is more potent when free from the antibody
25 portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter *et al.*), by hydrolysis of
30 derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn *et al.*), by

serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler *et al.*).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In
5 another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

10 A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato *et al.*), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih *et al.*). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a
15 liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur
20 atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison *et al.* discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous,
25 intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a breast tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a breast tumor polypeptide, polynucleotide encoding a breast tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a breast tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a breast tumor polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen *et al.*, *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a breast tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above

for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN- γ) is indicative of T cell activation (*see* Coligan *et al.*, Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been
5 activated in response to a breast tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Breast tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

10 For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a breast tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a breast tumor polypeptide, or a short peptide corresponding to an immunogenic portion
15 of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a breast tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a breast tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

20 PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

25 It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do
30 not cause a significant adverse effect upon contact with the target cells or host tissues.

The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or
5 DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal,
10 and intramuscular administration and formulation.

1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they
15 may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz *et al.*, 1997; Hwang *et al.*, 1998;
20 U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as
25 magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance,
30 tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup or elixir

may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even

intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will

be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-
5 1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

10 Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other
15 ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

20 The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can
25 also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of
30 dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art.

- 5 Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when
10 administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

15 3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.*, in U. S. Patent 5,756,353 and U.
20 S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a
25 polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the

introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

5 Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur *et al.*, 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for
10 intracellular bacterial infections and diseases). Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura,
15 1998; Chandran *et al.*, 1997; Margalit, 1995; U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions,
20 primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazsovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*,
25 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trials examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several
30 studies suggest that the use of liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4 μ m. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drug-bearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur *et al.* (1977; 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are

sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be easily made, as described (Couvreur *et al.*, 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.* 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

IMMUNOGENIC COMPOSITIONS

In certain preferred embodiments of the present invention, immunogenic compositions, or vaccines, are provided. The immunogenic compositions will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable

microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995).

5 Pharmaceutical compositions and immunogenic compositions within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition.

10 Illustrative immunogenic compositions may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are
15 well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that
20 expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch *et al.*, *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner *et al.*, *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner *et al.*, *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld *et al.*, *Science* 252:431-434, 1991; Kolls *et al.*, *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994;
30 Kass-Eisler *et al.*, *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman *et al.*, *Circulation* 88:2838-2848, 1993; and Guzman *et al.*, *Cir. Res.* 73:1202-1207, 1993.

Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer *et al.*, *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating
5 the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that an immunogenic composition may comprise both a polynucleotide and a polypeptide component. Such immunogenic compositions may provide for an enhanced immune response.

It will be apparent that an immunogenic composition may contain
10 pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

15 While any suitable carrier known to those of ordinary skill in the art may be employed in the compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or
20 intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres
25 (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No.
30 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the immunogenic compositions of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the immunogenic compositions provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN- γ , TNF α , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of an immunogenic composition as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will

increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; *see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato *et al.*, *Science* 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any immunogenic composition provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient. The compositions described herein may be

administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see, e.g.*, Coombes *et al.*, *Vaccine* 14:1429-
5 1438, 1996) and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

10 Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid
15 hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and
20 expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and immunogenic compositions to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells,
25 monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of
30 biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-
10 surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within an immunogenic composition (*see* Zitvogel *et al.*, *Nature Med.* 4:594-600, 1998).

15 Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF α to cultures of monocytes
20 harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF α , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

25 Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which
30 correlates with the high expression of Fc γ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high

expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a breast tumor protein (or portion or other variant thereof) such that the breast tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi *et al.*, *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the breast tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Immunogenic compositions and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, an immunogenic composition or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as breast cancer. Within such

methods, pharmaceutical compositions and immunogenic compositions are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and immunogenic compositions
5 may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and immunogenic compositions may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or
10 conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous
15 host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established
20 tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-
25 activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic
30 antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see, for example, Cheever et al., Immunological Reviews 157:177, 1997*).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and immunogenic compositions may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be

appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-
5 dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such immunogenic compositions should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in treated patients as compared to non-treated patients. In general, for pharmaceutical compositions and
10 immunogenic compositions comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 μ g to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the
15 active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a breast tumor protein generally correlate with an
20 improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

CANCER DETECTION AND DIAGNOSIS

In general, a cancer may be detected in a patient based on the presence
25 of one or more breast tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as breast cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided
30 herein generally permit detection of the level of antigen that binds to the agent in the

biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a breast tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

5 There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b)
10 detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

 In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a
15 detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a
20 polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length breast tumor
25 proteins and portions thereof to which the binding agent binds, as described above.

 The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a
30 plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S.

Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μ g, and preferably about 100 ng to about 1 μ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The

5 immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with breast cancer.

10 Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is

15 generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

20 The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method

25 employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme).

30 Enzyme reporter groups may generally be detected by the addition of substrate

(generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as breast cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett *et al.*, *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a

region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use breast tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such breast tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a breast tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a breast tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 μ g/ml). It may be desirable to incubate another aliquot of a T cell sample

in the absence of breast tumor polypeptide to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a breast tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a breast tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the breast tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a breast tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a breast tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477 479, 484, 486 and 489. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis *et al.*, *Cold Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple breast tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that

results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

The present invention further provides kits for use within any of the
5 above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a breast tumor protein. Such antibodies or fragments may be provided attached to a support
10 material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA
15 encoding a breast tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a breast tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or
20 container to facilitate the detection of a polynucleotide encoding a breast tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1
ISOLATION AND CHARACTERIZATION OF BREAST
TUMOR POLYPEPTIDES

5 This Example describes the isolation of breast tumor polypeptides from a breast tumor cDNA library.

 A cDNA subtraction library containing cDNA from breast tumor subtracted with normal breast cDNA was constructed as follows. Total RNA was extracted from primary tissues using Trizol reagent (Gibco BRL Life Technologies, Gaithersburg, MD) as described by the manufacturer. The polyA⁺ RNA was purified using an oligo(dT) cellulose column according to standard protocols. First strand cDNA was synthesized using the primer supplied in a Clontech PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, CA). The driver DNA consisted of cDNAs from two normal breast tissues with the tester cDNA being from three primary breast tumors.

15 Double-stranded cDNA was synthesized for both tester and driver, and digested with a combination of endonucleases (MluI, MscI, PvuII, SalI and StuI) which recognize six base pairs DNA. This modification increased the average cDNA size dramatically compared with cDNAs generated according to the protocol of Clontech (Palo Alto, CA). The digested tester cDNAs were ligated to two different adaptors and the subtraction was performed according to Clontech's protocol. The subtracted cDNAs were subjected to two rounds of PCR amplification, following the manufacturer's protocol. The resulting PCR products were subcloned into the TA cloning vector, pCRII (Invitrogen, San Diego, CA) and transformed into ElectroMax *E. coli* DH10B cells (Gibco BRL Life, Technologies) by electroporation. DNA was isolated from

20 independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division (Foster City, CA) Automated Sequencer Model 373A.

 Sixty-three distinct cDNA clones were found in the subtracted breast tumor-specific cDNA library. The determined one strand (5' or 3') cDNA sequences for the clones are provided in SEQ ID NO: 1-61, 72 and 73, respectively. Comparison

30 of these cDNA sequences with known sequences in the gene bank using the EMBL and GenBank databases (Release 97) revealed no significant homologies to the sequences

provided in SEQ ID NO: 14, 21, 22, 27, 29, 30, 32, 38, 44, 45, 53, 72 and 73. The sequences of SEQ ID NO: 1, 3, 16, 17, 34, 48, 57, 60 and 61 were found to represent known human genes. The sequences of SEQ ID NO: 2, 4, 23, 39 and 50 were found to show some similarity to previously identified non-human genes. The remaining clones
5 (SEQ ID NO: 5-13, 15, 18-20, 24-26, 28, 31, 33, 35-37, 40-43, 46, 47, 49, 51, 52, 54-56, 58 and 59) were found to show at least some degree of homology to previously identified expressed sequence tags (ESTs).

To determine mRNA expression levels of the isolated cDNA clones, cDNA clones from the breast subtraction described above were randomly picked and
10 colony PCR amplified. Their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were arrayed onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and
15 fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. Data was analyzed using Synteni provided GEMTOOLS Software. Of the seventeen cDNA clones examined, those of SEQ ID NO: 40, 46, 59 and 73 were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested
20 (breast, PBMC, colon, fetal tissue, salivary gland, bone marrow, lung, pancreas, large intestine, spinal cord, adrenal gland, kidney, pancreas, liver, stomach, skeletal muscle, heart, small intestine, skin, brain and human mammary epithelial cells). The clones of SEQ ID NO: 41 and 48 were found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested, with the exception of bone marrow. The clone
25 of SEQ ID NO: 42 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested except bone marrow and spinal cord. The clone of SEQ ID NO: 43 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of spinal cord, heart and small intestine. The clone of SEQ ID NO: 51 was found to be over-expressed in breast tumor and
30 expressed at low levels in all other tissues tested with the exception of large intestine. The clone of SEQ ID NO: 54 was found to be over-expressed in breast tumor and

expressed at low levels in all other tissues tested with the exception of PBMC, stomach and small intestine. The clone of SEQ ID NO: 56 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of large and small intestine, human mammary epithelia cells and SCID mouse-passaged breast tumor. The clone of SEQ ID NO: 60 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of spinal cord and heart. The clone of SEQ ID NO: 61 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of small intestine. The clone of SEQ ID NO: 72 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of colon and salivary gland.

The results of a Northern blot analysis of the clone SYN18C6 (SEQ ID NO: 40) are shown in Fig. 1. A predicted protein sequence encoded by SYN18C6 is provided in SEQ ID NO: 62.

Additional cDNA clones that are over-expressed in breast tumor tissue were isolated from breast cDNA subtraction libraries as follows. Breast subtraction libraries were prepared, as described above, by PCR-based subtraction employing pools of breast tumor cDNA as the tester and pools of either normal breast cDNA or cDNA from other normal tissues as the driver. cDNA clones from breast subtraction were randomly picked and colony PCR amplified and their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using the microarray technology described above. Twenty-four distinct cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested (breast, brain, liver, pancreas, lung, salivary gland, stomach, colon, kidney, bone marrow, skeletal muscle, PBMC, heart, small intestine, adrenal gland, spinal cord, large intestine and skin). The determined cDNA sequences for these clones are provided in SEQ ID NO: 63-87. Comparison of the sequences of SEQ ID NO: 74-87 with those in the gene bank as described above, revealed homology to previously identified human genes. No significant homologies were found to the sequences of SEQ ID NO: 63-73.

Three DNA isoforms for the clone B726P (partial sequence provided in SEQ ID NO: 71) were isolated as follows. A radioactive probe was synthesized from

B726P by excising B726P DNA from a pT7Blue vector (Novagen) by a BamHI/XbaI restriction digest and using the resulting DNA as the template in a single-stranded PCR in the presence of [α -32P]dCTP. The sequence of the primer employed for this PCR is provided in SEQ ID NO: 177. The resulting radioactive probe was used to probe a
5 directional cDNA library and a random-primed cDNA library made using RNA isolated from breast tumors. Eighty-five clones were identified, excised, purified and sequenced. Of these 85 clones, three were found to each contain a significant open reading frame. The determined cDNA sequence of the isoform B726P-20 is provided in SEQ ID NO: 175, with the corresponding predicted amino acid sequence being
10 provided in SEQ ID NO: 176. The determined cDNA sequence of the isoform B726P-74 is provided in SEQ ID NO: 178, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 179. The determined cDNA sequence of the isoform B726P-79 is provided in SEQ ID NO: 180, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 181.

15 Efforts to obtain a full-length clone of B726P using standard techniques led to the isolation of five additional clones that represent additional 5' sequence of B726P. These clones appear to be alternative splice forms of the same gene. The determined cDNA sequences of these clones are provided in SEQ ID NO: 464-468, with the predicted amino acid sequences encoded by SEQ ID NO: 464-467 being
20 provided in SEQ ID NO: 470-473, respectively. Using standard computer techniques, a 3,681 bp consensus DNA sequence (SEQ ID NO: 463) was created that contains two large open reading frames. The downstream ORF encodes the amino acid sequence of SEQ ID NO: 181. The predicted amino acid sequence encoded by the upstream ORF is provided in SEQ ID NO: 469. Subsequent studies led to the isolation of an additional
25 splice form of B726P that has 184 bp insert relative to the other forms. This 184 bp insert causes a frameshift that brings the down stream and upstream ORFs together into a single ORF that is 1002 aa in length. The determined cDNA sequence of this alternative splice form is disclosed in SEQ ID NO: 474, with the corresponding amino acid sequence being provided in SEQ ID NO: 475.

30 Further isolation of individual clones that are over-expressed in breast tumor tissue was conducted using cDNA subtraction library techniques described above. In particular, a cDNA subtraction library containing cDNA from breast tumors

subtracted with five other normal human tissue cDNAs (brain, liver, PBMC, pancreas and normal breast) was utilized in this screening. From the original subtraction, one hundred seventy seven clones were selected to be further characterized by DNA sequencing and microarray analysis. Microarray analysis demonstrated that the sequences in SEQ ID NO: 182-251 and 479 were 2 or more fold over-expressed in human breast tumor tissues over normal human tissues. No significant homologies were found for nineteen of these clones, including, SEQ ID NO: 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246 and 479, with the exception of some previously identified expressed sequence tags (ESTs). The remaining clones share some homology to previously identified genes, specifically SEQ ID NO: 181-184, 187-193, 195-198, 200-204, 206, 207, 209, 210, 212, 213, 217, 218, 220, 221, 223-225, 227-231, 233-235, 237-239, 242-244 and 247-251.

One of the cDNA clones isolated by PCR subtraction as described above (SEQ ID NO: 476; referred to as B720P) which was shown by microarray to be over-expressed in breast tumor tissues, was found to be identical to a known keratin gene. The full-length cDNA sequence of the known keratin gene is provided in SEQ ID NO: 477, with the corresponding amino acid sequence being provided in SEQ ID NO: 478. Primers were generated based on the sequence of SEQ ID NO: 477 and used to clone full-length cDNA from mRNA which was obtained from total RNA showing high expression of B720P in real-time PCR analysis. Products were then cloned and sequenced. The determined full-length cDNA sequence for B720P is provided in SEQ ID NO: 484, with the corresponding amino acid sequence being provided in SEQ ID NO: 485.

In further studies, a truncated form of B720P (referred to as B720P-tr) was identified in breast carcinomas. This antigen was cloned from mRNA derived from total breast tumor RNA that showed high expression of B720P-tr in real-time PCR analysis. mRNA was used to generate a pool of cDNA which was then used as a template to amplify the cDNA corresponding to B720P-tr by PCR. The determined cDNA sequence for B720P-tr is provided in SEQ ID NO: 486. B720P-tr has an ORF of 708 base pairs which encodes a 236 amino acid protein (SEQ ID NO: 487). The size of the transcript was confirmed by northern analysis.

Of the seventy clones showing over-expression in breast tumor tissues, fifteen demonstrated particularly good expression levels in breast tumor over normal

human tissues. The following eleven clones did not show any significant homology to any known genes. Clone 19463.1 (SEQ ID NO: 185) was over-expressed in the majority of breast tumors and also in the SCID breast tumors tested (refer to Example 2); additionally, over-expression was found in a majority of normal breast tissues.

5 Clone 19483.1 (SEQ ID NO: 216) was over-expressed in a few breast tumors, with no over-expression in any normal tissues tested. Clone 19470.1 (SEQ ID NO: 219) was found to be slightly over-expressed in some breast tumors. Clone 19468.1 (SEQ ID NO: 222) was found to be slightly over-expressed in the majority of breast tumors tested. Clone 19505.1 (SEQ ID NO: 226) was found to be slightly over-expressed in 50% of

10 breast tumors, as well as in SCID tumor tissues, with some degree of over-expression in found in normal breast. Clone 1509.1 (SEQ ID NO: 232) was found to be over-expressed in very few breast tumors, but with a certain degree of over-expression in metastatic breast tumor tissues, as well as no significant over-expression found in normal tissues. Clone 19513.1 (SEQ ID NO: 236) was shown to be slightly over-

15 expressed in few breast tumors, with no significant over-expression levels found in normal tissues. Clone 19575.1 (SEQ ID NO: 240) showed low level over-expression in some breast tumors and also in normal breast. Clone 19560.1 (SEQ ID NO: 241) was over-expressed in 50% of breast tumors tested, as well as in some normal breast tissues. Clone 19583.1 (SEQ ID NO: 245) was slightly over-expressed in some breast tumors,

20 with very low levels of over-expression found in normal tissues. Clone 19587.1 (SEQ ID NO: 246) showed low level over-expression in some breast tumors and no significant over-expression in normal tissues.

Clone 19520.1 (SEQ ID NO: 233), showing homology to clone 102D24 on chromosome 11q13.31, was found to be over-expressed in breast tumors and in

25 SCID tumors. Clone 19517.1 (SEQ ID NO: 237), showing homology to human PAC 128M19 clone, was found to be slightly over-expressed in the majority of breast tumors tested. Clone 19392.2 (SEQ ID NO: 247), showing homology to human chromosome 17, was shown to be over-expressed in 50% of breast tumors tested. Clone 19399.2 (SEQ ID NO: 250), showing homology to human Xp22 BAC GSHB-184P14, was

30 shown to be slightly over-expressed in a limited number of breast tumors tested.

In subsequent studies, 64 individual clones were isolated from a subtracted cDNA library containing cDNA from a pool of breast tumors subtracted with

cDNA from five normal tissues (brain, liver, PBMC, pancreas and normal breast). The subtracted cDNA library was prepared as described above with the following modification. A combination of five six-base cutters (MluI, MscI, PvuII, SalI and StuI) was used to digest the cDNA instead of RsaI. This resulted in an increase in the average insert size from 300 bp to 600 bp. The 64 isolated clones were colony PCR amplified and their mRNA expression levels in breast tumor tissue, normal breast and various other normal tissues were examined by microarray technology as described above. The determined cDNA sequences of 11 clones which were found to be over-expressed in breast tumor tissue are provided in SEQ ID NO: 405-415. Comparison of these sequences to those in the public database, as outlined above, revealed homologies between the sequences of SEQ ID NO: 408, 411, 413 and 414 and previously isolated ESTs. The sequences of SEQ ID NO: 405-407, 409, 410, 412 and 415 were found to show some homology to previously identified sequences.

In further studies, a subtracted cDNA library was prepared from cDNA from metastatic breast tumors subtracted with a pool of cDNA from five normal tissues (breast, brain, lung, pancreas and PBMC) using the PCR-subtraction protocol of Clontech, described above. The determined cDNA sequences of 90 clones isolated from this library are provided in SEQ ID NO: 316-404. Comparison of these sequences with those in the public database, as described above, revealed no significant homologies to the sequence of SEQ ID NO: 366. The sequences of SEQ ID NO: 321-325, 343, 354, 368, 369, 377, 382, 385, 389, 395, 397 and 400 were found to show some homology to previously isolated ESTs. The remaining sequences were found to show homology to previously identified gene sequences.

In yet further studies, a subtracted cDNA library (referred to as 2BT) was prepared from cDNA from breast tumors subtracted with a pool of cDNA from six normal tissues (liver, brain, stomach, small intestine, kidney and heart) using the PCR-subtraction protocol of Clontech, described above. cDNA clones isolated from this subtraction were subjected to DNA microarray analysis as described above and the resulting data subjected to four modified Gemtools analyses. The first analysis compared 28 breast tumors with 28 non-breast normal tissues. A mean over-expression of at least 2.1 fold was used as a selection cut-off. The second analysis compared 6

metastatic breast tumors with 29 non-breast normal tissues. A mean over-expression of at least 2.5 fold was used as a cut-off. The third and fourth analyses compared 2 early SCID mouse-passaged with 2 late SCID mouse-passaged tumors. A mean over-expression in the early or late passaged tumors of 2.0 fold or greater was used as a cut-off. In addition, a visual analysis was performed on the microarray data for the 2BT clones. The determined cDNA sequences of 13 clones identified in the visual analysis are provided in SEQ ID NO: 427-439. The determined cDNA sequences of 22 clones identified using the modified Gemtools analysis are provided in SEQ ID NO: 440-462, wherein SEQ ID NO: 453 and 454 represent two partial, non-overlapping, sequences of the same clone.

Comparison of the clone sequences of SEQ ID NO: 436 and 437 (referred to as 263G6 and 262B2) with those in the public databases, as described above, revealed no significant homologies to previously identified sequences. The sequences of SEQ ID NO: 427, 429, 431, 435, 438, 441, 443, 444, 445, 446, 450, 453 and 454 (referred to as 266B4, 266G3, 264B4, 263G1, 262B6, 2BT2-34, 2BT1-77, 2BT1-62, 2BT1-60, 61, 2BT1-59, 2BT1-52 and 2BT1-40, respectively) showed some homology to previously isolated expressed sequences tags (ESTs). The sequences of SEQ ID NO: 428, 430, 432, 433, 434, 439, 440, 442, 447, 448, 449, 451, 452 and 455-462 (referred to as clones 22892, 22890, 22883, 22882, 22880, 22869, 21374, 21349, 21093, 21091, 21089, 21085, 21084, 21063, 21062, 21060, 21053, 21050, 21036, 21037 and 21048, respectively), showed some homology to gene sequences previously identified in humans.

EXAMPLE 2

ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES OBTAINED BY PCR-BASED SUBTRACTION USING SCID-PASSAGED TUMOR RNA

Human breast tumor antigens were obtained by PCR-based subtraction using SCID mouse passaged breast tumor RNA as follows. Human breast tumor was implanted in SCID mice and harvested on the first or sixth serial passage, as described

in Patent Application Serial No. 08/556,659 filed 11/13/95, U.S. Patent No. 5,986,170. Genes found to be differentially expressed between early and late passage SCID tumor may be stage specific and therefore useful in therapeutic and diagnostic applications. Total RNA was prepared from snap frozen SCID passaged human breast tumor from
5 both the first and sixth passage.

PCR-based subtraction was performed essentially as described above. In the first subtraction (referred to as T9), RNA from first passage tumor was subtracted from sixth passage tumor RNA to identify more aggressive, later passage-specific antigens. Of the 64 clones isolated and sequenced from this subtraction, no significant
10 homologies were found to 30 of these clones, hereinafter referred to as: 13053, 13057, 13059, 13065, 13067, 13068, 13071-13073, 13075, 13078, 13079, 13081, 13082, 13092, 13097, 13101, 13102, 13131, 13133, 13119, 13135, 13139, 13140, 13146-13149, and 13151, with the exception of some previously identified expressed sequence tags (ESTs). The determined cDNA sequences for these clones are provided in SEQ ID
15 NO: 88-116, respectively. The isolated cDNA sequences of SEQ ID NO: 117-140 showed homology to known genes.

In a second PCR-based subtraction, RNA from sixth passage tumor was subtracted from first passage tumor RNA to identify antigens down-regulated over multiple passages. Of the 36 clones isolated and sequenced, no significant homologies
20 were found to nineteen of these clones, hereinafter referred to as: 14376, 14377, 14383, 14384, 14387, 14392, 14394, 14398, 14401, 14402, 14405, 14409, 14412, 14414-14416, 14419, 14426, and 14427, with the exception of some previously identified expressed sequence tags (ESTs). The determined cDNA sequences for these clones are provided in SEQ ID NO: 141-159, respectively. The isolated cDNA sequences of SEQ
25 ID NO: 160-174 were found to show homology to previously known genes.

Further analysis of human breast tumor antigens through PCR-based subtraction using first and sixth passage SCID tumor RNA was performed. Sixty three clones were found to be differentially expressed by a two or more fold margin, as determined by microarray analysis, i.e., higher expression in early passage tumor over
30 late passage tumor, or vice versa.. Seventeen of these clones showed no significant homology to any known genes, although some degree of homology with previously

identified expressed sequence tags (ESTs) was found, hereinafter referred to as 20266, 20270, 20274, 20276, 20277, 20280, 20281, 20294, 20303, 20310, 20336, 20341, 20941, 20954, 20961, 20965 and 20975 (SEQ ID NO: 252-268, respectively). The remaining clones were found to share some degree of homology to known genes, which
5 are identified in the Brief Description of the Drawings and Sequence Identifiers section above, hereinafter referred to as 20261, 20262, 20265, 20267, 20268, 20271, 20272, 20273, 20278, 20279, 20293, 20300, 20305, 20306, 20307, 20313, 20317, 20318, 20320, 20321, 20322, 20326, 20333, 20335, 20337, 20338, 20340, 20938, 20939, 20940, 20942, 20943, 20944, 20946, 20947, 20948, 20949, 20950, 20951, 20952,
10 20957, 20959, 20966, 20976, 20977 and 20978. The determined cDNA sequences for these clones are provided in SEQ ID NO: 269-314, respectively.

The clones 20310, 20281, 20262, 20280, 20303, 20336, 20270, 20341, 20326 and 20977 (also referred to as B820P, B821P, B822P, B823P, B824P, B825P, B826P, B827P, B828P and B829P, respectively) were selected for further analysis
15 based on the results obtained with microarray analysis. Specifically, microarray data analysis indicated at least two- to three-fold overexpression of these clones in breast tumor RNA compared to normal tissues tested. Subsequent studies led to the determination of the complete insert sequence for the clones B820P, B821P, B822P, B823P, B824P, B825P, B826P, B827P, B828P and B829P. These extended cDNA
20 sequences are provided in SEQ ID NO: 416-426, respectively.

EXAMPLE 3

SYNTHESIS OF POLYPEPTIDES

25 Polypeptides may be synthesized on an Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide.
30 Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol

(40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water
5 (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

EXAMPLE 4

10 ELICITATION OF BREAST ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of the breast-specific antigen B726P to elicit a cytotoxic T lymphocyte (CTL) response in peripheral blood lymphocytes
15 from normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of a normal donor by growth for five days in RPMI medium containing 10% human serum, 30 ng/ml GM-CSF and 30 ng/ml IL-4. Following five days of culture, DC were infected overnight with adenovirus expressing
20 recombinant B726P (downstream ORF; SEQ ID NO: 181) at an M.O.I. of 2.5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. CD8 positive cells were enriched for by the depletion of CD4 and CD14-positive cells. Priming cultures were initiated in individual wells of several 96-well plates with the cytokines IL-6 and IL-12. These cultures were restimulated in the presence of IL-2 using
25 autologous fibroblasts treated with IFN-gamma and transduced with B726P and CD80. Following three stimulation cycles, the presence of B726P-specific CTL activity was assessed in IFN-gamma Elispot assays (Lalvani et al., *J. Exp. Med.* 186:859-865, 1997) using IFN-gamma treated autologous fibroblasts transduced to express either B726P or an irrelevant, control, antigen as antigen presenting cells (APC). Of approximately 96
30 lines, one line (referred to as 6-2B) was identified that appeared to specifically recognize B726P-transduced APC but not control antigen-transduced APC. This

microculture was cloned using standard protocols. B726P-specific CTL were identified by Elispot analysis and expanded for further analysis. These CTL clones were demonstrated to recognize B726P-expressing fibroblasts, but not the control antigen MART-1, using chromium-51 release assays. Furthermore, using a panel of allogeneic
5 fibroblasts transduced with B726P in antibody blocking assays, the HLA restriction element for these B726P-specific CTL was identified as HLA-B*1501.

In order to define more accurately the location of the epitope recognized by the B726P-specific CTL clones, a deletion construct comprising only the N-terminal
10 half of B726P (B726Pdelta3') was constructed (a.a. 1-129) into the pBIB retroviral expression plasmid. This plasmid as well as other plasmids containing B726P were transfected into COS-7 cells either alone or in combination with a plasmid expressing HLA-B*1501. Approximately 48 hours after transfection, a B726P-specific CTL clone (1-9B) was added at approximately 10e4 cells per well. The wells were harvested the
15 next day and the amount of IFN-gamma released was measured by ELISA. The CTL responded above background (EGFP) to COS-7 cells that had been transfected with both B726P and HLA-B*1501. There was no response above background to COS-7 cells that had been transfected with B726P or HLA-B*1501 only. Importantly, a higher response was seen with COS-7 cells that had been transfected with HLA-B*1501 and
20 B726Pdelta3'. This result indicated that the epitope was likely to be located in the N-terminal region (a.a. 1-129) of B726P. This region was examined and amino acid sequences that corresponded to the HLA-B*1501 peptide binding motif (J. Immunol.1999,162:7277-84) were identified and synthesized. These peptides were pulsed at 10 ug/ml onto autologous B-LCL overnight. The next day the cells were
25 washed and the ability of the cells to stimulate the B726P-specific CTL clone 1-9B was assayed in a IFN-gamma ELISPOT assay. Of the eleven peptides tested, only one peptide, having the amino acid sequence SLTKRASQY (a.a. 76-84; SEQ ID NO: 488) was able to be recognized by the CTL. This result identifies this peptide as being a naturally-processed epitope recognized by this B726P-specific CTL clone.

EXAMPLE 5

PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST
BREAST TUMOR POLYPEPTIDES

5 Polyclonal antibodies against the breast tumor antigen B726P were prepared as follows.

The downstream ORF of B726P (SEQ ID NO: 181) expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37 °C in a shaking incubator. The next morning, 10 ml of the
10 overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and
15 the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell
20 pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to
25 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE
30 gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin, such as HiPrepQ (Biorad), was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another
5 SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The protein was then vialled after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of B726P antigen was combined with 100
10 micrograms of muramyl dipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4 °C for 12-24 hours followed by centrifugation.

Ninety-six well plates were coated with B726P antigen by incubating
15 with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 Microliters of BSA blocking buffer was added to the wells and incubated at room temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above
20 before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H₂SO₄
25 and read immediately at 450 nm. The polyclonal antibodies showed immunoreactivity to B726P.

EXAMPLE 6

PROTEIN EXPRESSION OF BREAST TUMOR ANTIGENS

The downstream ORF of B726P (SEQ ID NO: 181), together with a C-terminal 6X His Tag, was expressed in insect cells using the baculovirus expression system as follows.

The cDNA for the full-length downstream ORF of B726P was PCR amplified using the primers of SEQ ID NO: 480 and 481. The PCR product with the expected size was recovered from agarose gel, restriction digested with EcoRI and Hind II, and ligated into the transfer plasmid pFastBac1, which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBB726P was used to make recombinant bacmid DNA and virus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies, Gaithersburg, MD). High Five cells were infected with the recombinant virus BVB726P to produce protein. The cDNA and amino acid sequences of the expressed B726P recombinant protein are provided in SEQ ID NO: 482 and 483, respectively.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS

1. An isolated polypeptide, comprising at least an immunogenic portion of a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 under moderately stringent conditions; and

(c) complements of sequences of (a) or (b).

2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 or a complement of any of the foregoing polynucleotide sequences.

3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NOs: 176, 179, 181, 469-473, 475, 485, 487 and 488.

4. An isolated polynucleotide encoding at least 15 amino acid residues of a breast tumor protein, or a variant thereof that differs in one or more

substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484 and 486 or a complement of any of the foregoing sequences.

5. An isolated polynucleotide encoding a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 or a complement of any of the foregoing sequences.

6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489.

7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 under moderately stringent conditions.

8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.

9. An expression vector, comprising a polynucleotide according to any one of claims 4-8.

10. A host cell transformed or transfected with an expression vector according to claim 9.

11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a breast tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 or a complement of any of the foregoing polynucleotide sequences.

12. A fusion protein, comprising at least one polypeptide according to claim 1.

13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.

16. A fusion protein, comprising a first amino acid portion and a second amino acid portion wherein said first amino acid portion includes 9 or more

contiguous amino acids from mammaglobin as depicted by amino acids 1-93 of SEQ ID NO: 493; wherein said second amino acid portion includes 9 or more contiguous amino acids from B726P as depicted by SEQ ID NO: 475, SEQ ID NO: 469, or SEQ ID NO: 176; and wherein said first amino acid portion is connected to either the amino terminal or carboxy-terminal end of said second amino acid portion.

17. The fusion protein of claim 16 wherein said first amino acid portion is

selected from the group consisting of IDELKECFLNQTDETLNVE (amino acids 59-78 of SEQ ID NO: 493); TTNAIDELKECFLNQ (amino acids 55-69 of SEQ ID NO: 493); SQHCYAGSGCPLEENVISKTI (amino acids 13-33 of SEQ ID NO: 493); EYKELLQEFIDNATTNAID (amino acids 41-60 of SEQ ID NO: 493); KLLMVLMLA (amino acids 2-10 of SEQ ID NO: 493); QEFIDNATTNAI (amino acids 47-59 of SEQ ID NO: 493); and LKECFLNQTDETL (amino acids 62-74 of SEQ ID NO: 493).

18. The fusion protein of claim 16 wherein said second amino acid portion

includes 9 or more contiguous amino acids encoded by the combined upstream and downstream open reading frame (ORF) of B726P as depicted in SEQ ID NO: 475.

19. The fusion protein of claim 16 wherein said second amino acid portion

includes 9 or more contiguous amino acids encoded by the upstream ORF of B726P as depicted in from SEQ ID NO: 469.

20. The fusion protein of claim 16 wherein said second amino acid portion

includes 9 or more contiguous amino acids encoded by the downstream ORF of B726P as depicted in SEQ ID NO: 176.

21. The fusion protein of claim 16 wherein said second amino acid portion includes 9 or more contiguous amino acids from the amino acid sequence depicted by amino acids 1-129 of SEQ ID NO: 475.
22. The fusion protein of claim 16 as depicted in SEQ ID NO: 493.
23. The fusion protein of claim 16 as depicted in SEQ ID NO: 494.
24. The fusion protein of claim 16 as depicted in SEQ ID NO: 495.
25. An isolated polynucleotide encoding a fusion protein according to claim 12 or claim 16.
26. The fusion protein of claim 16 wherein said first amino acid portion is connected to the N-terminus of said second amino acid portion.
27. The fusion protein of claim 16 wherein said first amino acid portion is connected to the C-terminus of said second amino acid portion.
28. An isolated polynucleotide encoding a fusion protein according to claim 12 or claim 16.
29. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:
 - (a) a polypeptide according to claim 1;
 - (b) a polynucleotide according to claim 4;
 - (c) an antibody according to claim 11;
 - (d) a fusion protein according to claim 12 or claim 16; and
 - (e) a polynucleotide according to claim 28.
30. An immunogenic composition comprising an immunostimulant and at least one component selected from the group consisting of:
 - (a) a polypeptide according to claim 1;
 - (b) a polynucleotide according to claim 4;

- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12 or claim 16; and
- (e) a polynucleotide according to claim 28.

31. An immunogenic composition according to claim 30, wherein the immunostimulant is an adjuvant.

32. An immunogenic composition according to claim 30, wherein the immunostimulant induces a predominantly Type I response.

33. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 29.

34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an immunogenic composition according to claim 30.

35. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

36. A pharmaceutical composition according to claim 29, wherein the antigen presenting cell is a dendritic cell or a macrophage.

37. An immunogenic composition comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (a) sequences recited in SEQ ID NOs:1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486, and 489-492;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii);
in combination with an immunostimulant.

38. An immunogenic composition according to claim 37, wherein the immunostimulant is an adjuvant.

39. An immunogenic composition according to claim 37, wherein the immunostimulant induces a predominantly Type I response.

40. An immunogenic composition according to claim 37, wherein the antigen-presenting cell is a dendritic cell.

41. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii) encoded by a polynucleotide recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

and thereby inhibiting the development of a cancer in the patient.

42. A method according to claim 41, wherein the antigen-presenting cell is a dendritic cell.

43. A method according to any one of claims 33, 34 and 41, wherein the cancer is breast cancer.

44. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

45. A method according to claim 44, wherein the biological sample is blood or a fraction thereof.

46. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 44.

47. A method for stimulating and/or expanding T cells specific for a breast tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) sequences recited in SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

(ii) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(iii) complements of sequences of (i) or (ii);

- (b) polynucleotides encoding a polypeptide of (a); and
 - (c) antigen presenting cells that express a polypeptide of (a);
- under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

48. An isolated T cell population, comprising T cells prepared according to the method of claim 47.

49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 49.

50. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that expresses a polypeptide of (i);

such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

51. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that express a polypeptide of (i);

such that T cells proliferate;

(b) cloning at least one proliferated cell to provide cloned T cells; and

(c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

52. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

53. A method according to claim 52, wherein the binding agent is an antibody.

54. A method according to claim 53, wherein the antibody is a monoclonal antibody.

55. A method according to claim 52, wherein the cancer is breast cancer.

56. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

57. A method according to claim 56, wherein the binding agent is an antibody.

58. A method according to claim 57, wherein the antibody is a monoclonal antibody.

59. A method according to claim 56, wherein the cancer is a breast cancer.

60. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

61. A method according to claim 60, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

62. A method according to claim 60, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

63. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

64. A method according to claim 63, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

65. A method according to claim 63, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

66. A diagnostic kit, comprising:

- (a) one or more antibodies according to claim 11; and
- (b) a detection reagent comprising a reporter group.

67. A kit according to claim 66, wherein the antibodies are immobilized on a solid support.

68. A kit according to claim 66, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

69. A kit according to claim 66, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

70. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325,

343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotides.

71. A oligonucleotide according to claim 70, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489-492.

72. A diagnostic kit, comprising:

- (a) an oligonucleotide according to claim 71; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

SYN18C6 NORTHERN BLOT

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1.35 kb —————→

0.24 kb —————→

Fig. 1

SEQUENCE LISTING

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 Jiang, Yuqiu
 Dillon, Davin C.
 Mitcham, Jennifer L.
 Xu, Jiangchun
 Harlocker, Susan L.
 Hepler, William T.

<120> COMPOSITIONS AND METHODS FOR THE THERAPY AND
 DIAGNOSIS OF BREAST CANCER

<130> 210121.47002PC

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tccacaaata	ctgaggtata	gcctgcatgc	cactaaaaat	aacaaagggt	tcaggggtgg	180
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<210> 25
 <211> 302
 <212> DNA
 <213> Homo sapien

<400> 25						
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tctgcaaagt	tcagcttcct	tcccaggtc	tctgtgcaact	ctgtcttgga	tgctctgggg	180
agctcatggg	tggaggagtc	tccaccagag	ggaggctcag	gggactgggt	gggccaggga	240
tgaatatttg	agggataaaa	attgtgtaag	aagccaaaga	aattggtagt	aggggggaga	300
ac						302

<210> 26
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 26						
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agaactgcac	tggcctctcc	tgctgcctga	tttatctgtg	cagccttttc	tgcttcggag	180
gccaggatct	gggctgttt	cttccttct	gccacattga	tggccgactc	tcgggtcccc	240
tcagactcta	gaactgtggc	ccgtttccgc	cgctctgcct	ccacctgcat	ctgcatagac	300
t						301

<210> 27
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 27						
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tcaaattgaa	atcatcttcc	ctctgtacag	attgcaatat	ctgataatac	cctcaacttt	180
cttgggtgcaa	attaattgcc	tggtactcac	agtcacagtgt	taacaggcaa	taatggtgtg	240
attccagagg	agaggactag	gtggcaggaa	aataaatgag	attagcagta	tttgacttgg	300
a						301

<210> 28
 <211> 286
 <212> DNA
 <213> Homo sapien

<400> 28
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 atccttagag gaagagaggg gtaaggatg aaagtaactg aaggaccgca agacgggtat 120
 gtcccttggt caccaaatgg tcaaagggtc aaagatcgga ggaggtcagg gggtaacgca 180
 ggaacagggtg agggcggttc gccctctctc cctctcccct tttcaacctc ttaatcactg 240
 gctaactcgc gacctcatgg gttaattcgt aagcttacac gcgttg 286

<210> 29
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 29
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 ttttcctttg ttcaaaggat ttattcctac catttcacaa atccgaaaat aattgaggaa 120
 acagggttaca tcattccaat ttgccttggt gtttgaagag tctctcatgg tggcacagtc 180
 ctccagggtg gctatgttgt tgggtcccc tacatcccag aagctcagag actttgtcaa 240
 aggtgtgccc tccaccatt gccactgacc ctgcacaacc tggcttgaca gtccaataaa 300
 a 301

<210> 30
 <211> 332
 <212> DNA
 <213> Homo sapien

<400> 30
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 cacctagtcc tctctctggt aatcacacca ttattgcctg ttaacactgg actgtgagta 120
 ccagggaatt aatttgacc aagaaagttg agggattat cagatattgc aatctgtaca 180
 gagggaagat gatttcaatt tgatttcaac ttaaccttca tctttgtctg ttaacactaa 240
 tagagggtgt ctaataaaat ggtcaaattt gtgatctcat ttgttataac tagcactctt 300
 ttcacagatg tgatgactga tttccagcag ac 332

<210> 31
 <211> 141
 <212> DNA
 <213> Homo sapien

<400> 31
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 ttctatttgc aggggttcag ggagggttc aggggttcag ggagggtct tgtccacaa 120
 ccgggggaag ggagaggga c 141

<210> 32
 <211> 201
 <212> DNA
 <213> Homo sapien

<400> 32
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 aatctgtcat ctaccttaaa gagagaaaaa agatggaaca taggccacc tagtttcatc 120
 catccacctt cataaccaac atagatgtga ggtccactgc actgatagcc agactgcctg 180
 gggtaaacct tttcaggag g 201

<210> 33
 <211> 181
 <212> DNA
 <213> Homo sapien

<400> 33
 tttcaaaaaca ctcatatgtt gcaaaaaaca catagaaaaa taaagtttgg tgggggtgct 60
 gactaaactt caagtcacag acttttatgt gacagattgg agcagggttt gttatgcatg 120

tagagaaccc aaactaattt attaaacagg atagaaacag gctgtctggg tgaaatgggt 180
c 181

<210> 34
<211> 151
<212> DNA
<213> Homo sapien

<400> 34
atgtcctgca cagtatacgt tggacctctg ggctgaacc agggtagca tcaaggcccc 60
catttctcct caccacgggg tcgcttgta gctccaagaa ccagtctggc cccactgaga 120
acttttcagt cgagggcctg atgaatcttg g 151

<210> 35
<211> 291
<212> DNA
<213> Homo sapien

<400> 35
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agctttaaca cgtgtaatct gcagtcctta acagtggcgt aattgtacgt acctgttggt 120
tttcagtttg tttttcacct ataatgaatt gtaaaaacaa acatacttgt ggggtctgat 180
agcaaacata gaaatgatgt atattgtttt ttgttatcta tttattttca tcaatacagt 240
attttgatgt attgcaaaaa tagataataa tttatataac aggttttctg t 291

<210> 36
<211> 201
<212> DNA
<213> Homo sapien

<400> 36
ctgatacaat tataataacg gttccctgaa ccttttagag tgcaattaag aacaaaaact 60
aaattttggt tacatgaata tggaataaat acaataatca aaatatgact ctccctaaaa 120
gtgaaacaca caagccaatc cggaaactgt gtgcgaaaga taaaatcgag aaaggcaagg 180
tttcggtagg aggacgcgat g 201

<210> 37
<211> 121
<212> DNA
<213> Homo sapien

<400> 37
catcacactg gcggccgctc gagcatgcat ctagagggcc caattcgccc tataatgagt 60
cgtattacaa ttcactggcc gtcgttttac aacgtcgtga ctgggaaaac cctggcggtta 120
c 121

<210> 38
<211> 200
<212> DNA
<213> Homo sapien

<400> 38
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gataaacacca cacatagaac attataatta cacacaaatt tatggtaaaa gaattaatat 180
gctgtctggt gctgctgtta 200

<210> 39
<211> 760
<212> DNA
<213> Homo sapien

<400> 39

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gatctggaaa	tacttgaggt	tattacatac	tagattagct	tctaattgtga	accatttttc	120
ttttaacagt	gatcaaatta	ttatttcgaa	gttaatcggt	cccttggtgg	ctgcatacac	180
atcgcatata	caaacatact	gttgtatttt	ttcccagttt	tgtttggtta	tgccaccaca	240
gtcatcccca	gggtctatac	atactatggt	tcaactgtat	tatttgccat	ttttggcatt	300
agaatgcttc	gggaaggctt	aaagatgagc	cctgatgagg	gtcaagagga	actggaagaa	360
gttcaagctg	aattaaagaa	gaaagatgaa	gaagtaagcc	atggcactgt	tgatctggac	420
caaaaaggca	ctcaactagg	aataaacact	ctacagaggt	ttctcagtgg	ccccatctgt	480
gtgatatcg	gggctacaca	aaaatagctt	cttttgcttt	gttctgttct	tatacctgtc	540
tgtgatctga	cttgggggtt	gtgtgaatgt	agtagagaaa	ggaagctgac	agatgaatac	600
tgaacacag	taatcagttt	ccttaattag	gttgattata	agctcctgaa	aagcaggaac	660
tgtattttat	aattttacct	gtttctcccg	tggtgtctag	gatagtaagt	gagcagagca	720
gtaaatactg	tttggtttgt	tcagacctgc	ccgggcggcc			760

<210> 40

<211> 452

<212> DNA

<213> Homo sapien

<400> 40

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tttattaaca	ggaattttga	ttcttcaagg	aagtggctca	atttcaattt	caggtgacca	120
ggttttcgt	gacttttctt	tcttgtttac	ttttcgctag	gaaggggagt	tgtaggggca	180
gattcaggt	ttggaatagg	aaaattacgt	ctaaaccatg	gaaatcttgg	aaatggaatt	240
gggtggaagt	ggcgaaatgg	atatgggtaa	gggaacacaa	aaaaccctga	agctaattca	300
tgcgtgtcac	tgatacttct	tttttctcgt	tcctggctct	gagagactgg	gaaaccaaca	360
gccactgcca	agatggctgt	gatcaggagg	agaactttct	tcactctcaa	cgtttcagtc	420
agttctttct	ctcacctcgg	ccgcgaccac	gc			452

<210> 41

<211> 676

<212> DNA

<213> Homo sapien

<400> 41

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aagatacata	gcaatgatag	caggttttctt	tttaaagctt	agtattaata	ttaaattattt	120
ttccccattt	aaattttaca	ttacttgcca	agaaaaaaaa	aaaattaaaa	ctcaagttac	180
ttgaagcctg	gacacacttc	catgattagc	cgggctaggt	aaaagttggt	ggctttattc	240
ttcctgctct	ataagcagat	ccaggcccta	gaaagatggg	accagggtat	ataattgttt	300
ttgaaaagt	tgctacaaaa	atggatggcc	tggtataagc	caggatacaa	agttaaggat	360
gggggtaagg	gagggacatt	ttcttccaga	agaaaagaca	gaattttctga	agagtccag	420
tccataattt	tcccaaatg	gttggaggag	agggtaaaat	ctcaacatga	gtttcaaagt	480
actgtctctg	tgaggggccg	gtagatgcct	tgctgaggag	ggatggctaa	tttgaccat	540
gccccatccc	cagctaggag	aatggaaatg	gaaacttta	ttgccagtg	gggtgtgaaag	600
tgggctgaag	cttggttggt	actgaattct	ctaagaggtt	tcttctagaa	acagacaact	660
cagacctgcc	cgggcg					676

<210> 42

<211> 468

<212> DNA

<213> Homo sapien

<400> 42

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ctgagcctca	gtctccctcc	cttggggcct	atgcagaggt	ccacaacaca	cagattttgag	120
ctcagccctg	gtgggcagag	aggtagggat	ggggctgtgg	ggatagtga	gcacgcgaat	180
gtaagactcg	ggattagtag	acacttgttg	atgaatggaa	atgtttacag	atccccaaagc	240
ctggcaagg	aattttctca	actccctgcc	ccccagccct	ccttatcaaa	ggacaccatt	300
ttggcaagct	ctatgaccaa	ggagccaaac	atcctacaag	acacagtga	catactaatt	360
aaaaccccct	gcaaaagcca	gcttgaaacc	ttcacttagg	aacgtaatcg	tgtcccctat	420

cctacttccc cttcctaatt ccacagacct gcccgggcgg ccgctcga 468

<210> 43
<211> 408
<212> DNA
<213> Homo sapien

<400> 43
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ttcatttcag gagagcagca gttaaaccgg tggattttgt agttaggaaac ctggggttcaa 120
acctctttcc actaattggc tatgtctctg gacagttttt tttttttttt ttttttttaa 180
acctttctg aactttcact ttctatggct acctcaaaga attgttggtga ggcttgagat 240
aatgcatttg taaagggctc gccagatagg aagatgctag ttatggattt acaaggttgt 300
taaggctgta agagtctaaa acctacagtg aatcacaatg catttaccoc cactgacttg 360
gacataagtg aaaactagcc cgaagtctct ttttcaaatt acttacag 408

<210> 44
<211> 160
<212> DNA
<213> Homo sapien

<400> 44
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ctctctgtgc tacaatgatt gcaccttctc acgcaacact ccaaccagga ctttcaacta 120
caacttctcc gctttggcaa acaccgtcac tcttgctgga 160

<210> 45
<211> 231
<212> DNA
<213> Homo sapien

<400> 45
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ccccataaag tcgatcagca aggctgacag gctgtgagga aaccccgcc ttgtagcctg 120
tcacctctgg ggggatgatg actgcctggc agacgtaggc tgtgatagat ttgggagaaa 180
acctgactca ccctcaggaa tccggaggtc ggtgacattg tcggtgcaca c 231

<210> 46
<211> 371
<212> DNA
<213> Homo sapien

<400> 46
cccgggcagg tctgtgtaac atgccaaaggc tttgcacttt ctgcagagca gttttttatt 60
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ctgtatatgc agaattcttt ccctaaatac tgcttcgtcc catgtctgaa ggcgtaaaaat 180
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cattactagt cagaaggaag cacttgctac ctcttgctct tcctctgcct ctgggtttgga 300
tcattttgat gacattgcc acattactca tgaaggatga caagattgca ctgtgcaatg 360
tcaattgcct t 371

<210> 47
<211> 261
<212> DNA
<213> Homo sapien

<400> 47
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catgcacgaa tgaagatgc tctggattac ttgaaagact tcttcagcaa tgtccgagca 120
gcaggattcg atgagattga gcaagatctt actcagagat ttgaagaaaa gctgcaggaa 180
ctagaaagtg tttccaggga tcccagcaat gagaatccta aacttgaaga cctctgcttc 240
atcttacaag aagagtacca c 261

11

<210> 48
 <211> 701
 <212> DNA
 <213> Homo sapien

<400> 48
 cgagcggccc cggggcaggc ccaattagta caagtctcat gatataatca ctgcctgcat 60
 acatatgcac agatccagtt agtgagtttg tcaagcttaa tctaattggg taagtctcaa 120
 agagattatt attcttgatg ttgtctttgt attggctaac aaatgtgcag aggtaataca 180
 tatgtgatgt ccgatgtctc tgtctttttt ttgtcttta aaaaataatt ggcagcaact 240
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 tttctttttg aaaggagag aattgaccat ttattattgt gatgtttaag ttataactta 360
 ttgagcactt ttagtagtga taactgtttt taaacttgcc taataccttt cttgggtatt 420
 gtttgaatg tgacttattt aacccctttt tttgtttgtt taagttgctg ctttaggtta 480
 acagcgtggt ttagaagatt taaatttttt tcctgtctgc acaattagtt attcagagca 540
 agagggcctg attttataga agccccttga aaagaggtcc agatgagagc agagatacag 600
 tgagaaatta tgtgatctgt gtgtgtgtgg aagagaattt tcaatatgta actacggagc 660
 tgtagtgcc a ttagaaactg tgaatttcca aataaatttg a 701

<210> 49
 <211> 270
 <212> DNA
 <213> Homo sapien

<400> 49
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 tatggaaata gatttttgtg cagctcaatt tatgcagaga ttaaatagaca tcataatact 180
 ggatgaaaac ttgatagaa ttctgattaa atagtgggtc tgtttcacat gtgcagtttg 240
 aagtatttaa attaaccact cttttcacag 270

<210> 50
 <211> 271
 <212> DNA
 <213> Homo sapien

<400> 50
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 acaataaaaa gttgaacatg cgcataatca tgcatttcac agaagattag taaaactgat 180
 ggcaacttca gaattatttc atgaagggtg caaacagctc ttaccacaat tttcccatgg 240
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<210> 51
 <211> 241
 <212> DNA
 <213> Homo sapien

<400> 51
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 aatggcttat ccccacggcc atgtaagtta ccatgcctgt ctccctccctc ctacacattt 120
 ccagctcctg ctgcagttat tctacagaa gctgccattt accagccctc tgtgattttg 180
 aatccacgag cactgcaggc cctccacagc gttactacct agcaggcact cagctcttca 240
 t 241

<210> 52
 <211> 271
 <212> DNA
 <213> Homo sapien

<400> 52

12

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tgcatgctgc	ttgctgtaag	ttacgatttg	gcttcactag	ctcaaatttt	ttcactccac	180
caaaagataa	ggcacaggcc	cgtttgtcca	atcaagtttg	ctgaaaatac	tgacagcctga	240
gtgtagacaa	acttcccctg	aatttgctag	a			271

<210> 53

<211> 493

<212> DNA

<213> Homo sapien

<400> 53

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atggattaac	caaaaaatgc	attactgcct	ttggcacact	gtcttgaata	ttctttctga	120
caatgagaaa	atatgattta	atggagtcgt	tcaataacct	cacaatctcg	ctgttccgag	180
cagatagttt	tcgtgccaac	aggaactggc	acatctagca	ggttcacggc	atgacctttt	240
tgtggactgg	ctggcataat	tggaatgggt	tttgattttt	cttctgctaa	taactcttca	300
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ctccaacccc	accacctcca	gatgcaacct	tgtctcgtga	tacagacctg	cccgggcggc	420
cctcaagggc	gaattctgca	gatatccatc	acactggcgg	ccgctcgagc	atgcatctag	480
agggccaat	tcg					493

<210> 54

<211> 321

<212> DNA

<213> Homo sapien

<400> 54

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actgaatgtc	aataaactct	gtgattttgt	taggaagtaa	aactgggagc	tatttagcca	120
ctggtaagct	tctgaggtga	aggattcagg	gacatctcgt	ggaacaaaac	ctccccactg	180
gactttctct	ctggagatac	ccttttgaat	atacaatggc	cttggtcac	taggtttaaa	240
tacaaacaag	tctgaaacct	actgaagact	gagagattgc	agcaatattc	tctgaattag	300
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<210> 55

<211> 281

<212> DNA

<213> Homo sapien

<400> 55

ttgcaaatga	aactgtggat	gtataataag	aaaacacaag	ggttttattct	taacactaaa	60
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gaacagccca	ccttggttac	agctagcaaa	gatggttact	tcaaagtatg	gatattaaca	180
gatgactctg	acataataca	aaaagctgtt	ggctggacct	gtgactttgt	tggtagttat	240
cacaagtatc	aagcaactaa	ctgttgtttc	tccgaagatg	g		281

<210> 56

<211> 612

<212> DNA

<213> Homo sapien

<400> 56

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taccctagcc	tgacactgtc	ctcatctctg	caaagttcag	cttccttccc	caggctctctg	180
tgccactctg	tcttggatgc	tctggggagc	tcatgggttg	aggagtctcc	accagaggga	240
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caagaatttg	gtagtgggg	gagaacagag	aggagctggg	ctatgggaaa	tgatttgaat	360
aatggagctg	ggaatatggc	tggatatctg	gtactaaaaa	agggtcttta	agaacctact	420
tcctaattct	ttccccaatc	caaaccatag	ctgtctgtcc	agtgctctct	tcctgcctcc	480
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gcagggttg gggagaggct gaggagagtg tgacatgtgg ggagaggacc agacctgccc 600
ggcgggccgt cg 612

<210> 57
<211> 363
<212> DNA
<213> Homo sapien

<400> 57
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gacaagacat ttgacttccc tttctccttg tctataaaat gtggacagtg gacgtctgtc 120
acccaagaga gttgtgggag acaagatcac agctatgagc acctcgcacg gtgtccagga 180
tgacacgac aatccatgat gcgttttctc cccttacgca ctttgaaacc catgctagaa 240
aagtgaatac atctgactgt gctccactcc aacctccagc gtggatgtcc ctgtctgggc 300
cctttttctg ttttttattc tatgttcagc accactggca ccaaatacat ttttaattcac 360
cga 363

<210> 58
<211> 750
<212> DNA
<213> Homo sapien

<400> 58
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ctgcgccctt ctcccaactc gcgtgcctca cagaaccag gtgctgcaca gccccgagat 120
gtggcccttc ttcaggaaag agcaaataag ttgggtccaag tacttgatgc ttaaggata 180
cacaaggtg cccatcaagc gctcagaaat gctgagagat atcatccgtg aatacactga 240
tgtttatcca gaaatcattg aacgtgcatg ctttgtccta gagaagaaat ttgggattca 300
actgaaagaa attgacaaaag aagaacacct gtatatctc atcagtaccc ccgagtcctt 360
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gggtgtcatc ttcataaatg gcaaccgtgc cagtgaggct gtcttttggg aggcactacg 480
caagatggga ctgcgtcctg ggggtgagaca tccctccctc tggagatcta aggaaactc 540
tcacctatga gtttgtaaag cagaaatacc tggactacag acgagtgcac aacagcaacc 600
ccccggagta tgagttctc tggggcctcc gtccctacca tgagactagc aagatgaaaa 660
tgctgagatt cattgcagag gttcagaaaa gagaccctcg tgactggact gcacagttca 720
tggaggctgc agatgaggac ctgcccgggc 750

<210> 59
<211> 505
<212> DNA
<213> Homo sapien

<400> 59
tgccgcgccg ggcaggtcca gtctacaagc agagcactct catggggagc accagatgag 60
ttccagccgc agttctttta taagctttaa gtgcctcatg aagacgcgag gatctcttcc 120
aagtgcacac tggtcacatc agggcacatt cagcagcaga agtctgtttc cagtatagtc 180
cttgggtatg ctaaattcca ctgtcccttt ctacagcagc aataatccat gataaattct 240
gtacaacact gtagtcaata acagcagcac cagacagcat attaatctt ttaccataaaa 300
tttgtgtgta attataatgt tctatgtgtg gtgttatcaa aagaatcact gtgtctctaa 360
atatcatata tgtatgtctg gataaataca ttgctgtaca acatctcaa catgcaggtc 420
atgctctaag acttggggat atagagtaat acatgtttcg tggacctcgg ccgcgaccac 480
gctaagggcg aattctgcag atatc 505

<210> 60
<211> 520
<212> DNA
<213> Homo sapien

<400> 60
cgtgggtcgcg gccaggtcc tcaggacaag gaaacaggta tcagcatgat ggtagcagaa 60
accttatcac caaggtgcag gagctgactt cttccaaaaga gttgtggttc cgggcagcgg 120
tcattgcctg cccttgctgg agggctgatt ttagtgttgc ttattatgtt gccctgag 180

14

```

atgcttcgaa gtgaaaataa gaggctgcag gatcagcggc aacagatgct ctcccgtttg 240
cactacagct ttcacggaca ccattccaaa aaggggcagg ttgcaaagtt agacttgga 300
tgcatgggtgc cggtcagtg gcacgagaac tgctgtctga cctgtgataa aatgagacaa 360
gcagacctca gcaacgataa gatcctctcg cttgttctact ggggcatgta cagtgggcac 420
gggaagctgg aattcgtatg acggagtctt atctgaacta cacttactga acagcttgaa 480
ggacctgccc gggcgggccc tcgaaagggg cgaattctgc 520

```

<210> 61
 <211> 447
 <212> DNA
 <213> Homo sapien

```

<400> 61
agagaggtgt ttttattctt tggggacaaa gccgggttct gtgggtgtag gattctccag 60
gttctccagg ctgtagggcc cagaggctta atcagaattt tcagacaaaa ctggaacctt 120
tcttttttcc cgttggttta tttgtagtcc ttgggcaaac caatgtcttt gttcgaaaga 180
gggaaaaataa tccaaacgtt tttcttttaa cttttttttt aggttcaggg gcacatgtgt 240
aggcttgcta tataggtaaa ttgcatgtca ccagggtttg ttgtacagat tatttcatca 300
tccagataaa aagcatagta cdagataggt agttttttga tcctcaccct ctttccatgc 360
tccgacctca ggtaggccc agtgtctgac ctgcccggcg gcccgctcga aagggccaat 420
tctgcagata tccatcacac tggccgg 447

```

<210> 62
 <211> 83
 <212> PRT
 <213> Homo sapien

```

<400> 62
Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val Gly
1      5      10      15
Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser Asp
20      25      30
Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr Pro
35      40      45
Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe Arg
50      55      60
Arg Asn Phe Pro Ile Pro Ser Ala Pro Thr Thr Pro Leu Pro
65      70      75      80
Ser Glu Lys

```

<210> 63
 <211> 683
 <212> DNA
 <213> Homo sapien

```

<400> 63
acaaagattg gtagctttta ttttttttta aaaatgctat actaagagaa aaaacaaaag 60
accacaacaa tattccaaat tataggttga gagaatgtga ctatgaagaa agtattctaa 120
ccaactaaaa aaaatattga aaccactttt gattgaagca aaatgaataa tgctagattt 180
aaaaacagtg tgaaatcaca ctttggctctg taaacatatt tagctttgct tttcattcag 240
atgtatacat aaacttattt aaaatgtcat ttaagtgaac cattccaagg cataataaaa 300
aaagwggtag caaatgaaaa ttaaagcatt ttttttggtta gttcttcaat aatgatrcga 360
gaaactgaat tccatccagt agaagcatct ctttttgggt aatctgaaca agtrccaacc 420
cagatagcaa catccactaa tccagcacca attccttcac aaagtccttc cacagaagaa 480
gtgcgatgaa tattaattgt tgaattcatt tcagggcttc cttggtccaa ataaattata 540
gcttcaatgg gaagaggtcc tgaacattca gctccattga atgtgaaata ccaacgtga 600
cagcatgcat ttctgcattt tagccgaagt gagccactga acaaaactct tagagcacta 660
tttgaacgca tctttgtaaa tgt 683

```

<210> 64
 <211> 749

<212> DNA
 <213> Homo sapien
 <220>
 <221> misc_feature
 <222> (1)...(749)
 <223> n = A,T,C or G

<400> 64
 ctgttcattt gtccgccagc tcctggactg gatgtgtgaa aggcatacaca tttccatttt 60
 cctccgtgta aatgttttat gtgttcgcct actgatccca ttcgttgctt ctattgtaaa 120
 tatttgcatt ttgtatttat tatctctgtg ttttccccct aaggcataaa atggtttact 180
 gtgttcattt gaacccattt actgatctct gttgtatatt tttcatgccca ctgctttgtt 240
 ttctcctcag aagtcgggta gatagcattt ctatcccatc cctcacgtta ttggaagcat 300
 gcaacagtat ttattgtctca gggctctctg cttaaaactg aggaaggtcc acattcctgc 360
 aagcattgat tgagacattt gcacaatcta aaatgtaagc aaagtaagtc attaaaaata 420
 caccctctac ttgggcttta tactgcatac aaatttactc atgagccttc ctttgaggaa 480
 ggatgtggat ctccaaataa agatttagtg tttattttga gctctgcatc ttancaagat 540
 gatctgaaca cctctccttt gtatcaataa atagccctgt tattctgaag tgagaggacc 600
 aagtatatga aaatgctgac atctaaaact aaataaatag aaaacaccag gccagaacta 660
 tagtcatact cacacaaagg gagaaattta aactcgaacc aagcaaaagg cttcacggaa 720
 atagcatgga aaaacaatgc ttccagtgg 749

<210> 65
 <211> 612
 <212> DNA
 <213> Homo sapien

<400> 65
 acagcagcag tagatggctg caacaacctt cctcctaccc cagcccagaa aatattttctg 60
 cccaccccca ggatccggga ccaaaataaa gagcaagcag gccccttca ctgaggtgct 120
 gggtagggct cagtgcacac ttactgtgct ttgagaaaga ggaaggggat ttgtttggca 180
 ctttaaaaat agaggagtaa gcaggactgg agaggccaga gaagatacca aaattggcag 240
 ggagagacca tttggcgcca gtcccctagg agatgggagg agggagatag gtatgagggg 300
 aggcgctaag aagagtagga ggggtccact ccaagtggca ggggtgctgaa atgggctagg 360
 accaacagga cactgactct aggtttatga cctgtccata cccgttccac agcagctggg 420
 tgggagaaat caccattttg tgacttctaa taaaataatg ggtctaggca acagttttca 480
 atggatgcta aaacgattag gtgaaaagtt gatggagaa ttttaattcag ggggaattagg 540
 ctgataccat ctgaaacat ttggcatcat taaaaatgtg acaacctggt ggctgccagg 600
 gaggaagggg ag 612

<210> 66
 <211> 703
 <212> DNA
 <213> Homo sapien

<400> 66
 tagcgtggtc gcggccgagg tacattgatg ggctggagag cagggttggc agcctgttct 60
 gcacagaacc aagaattaca gaaaaaagtc caggagctgg agaggcaca catctccttg 120
 gtagctcagc tccgccagct gcagacgcta attgctcaaa cttccaacaa agctgccag 180
 accagcactt gtgttttgat tcttcttttt tccctggctc tcatcatcct gccagcttc 240
 agtccattcc agagtgcacc agaagctggg tctgaggatt accagcctca cggagtgact 300
 tccagaaata tctgaccca caaggacgta acagaaaatc tggagaccca agtggtagag 360
 tccagactga gggagccacc tggagccaag gatgcaaatg gctcaacaag gacactgctt 420
 gagaagatgg gaggggaagcc aagacccagt gggcgcatcc ggtccgtgct gcatgcagat 480
 gagatgtgag ctggaacaga ccttcctggc ccacttcctg atcacaagga atcctgggct 540
 tccttatggc tttgcttccc actgggattc ctacttaggt gtctgccctc aggggtccaa 600
 atcacttcag gacaccccaa gagatgtcct ttagtctctg cctgaggcct agtctgcatt 660
 tgtttgcata tatgagaggg tacctgcccc ggccggccgct cga 703

<210> 67
 <211> 1022

16

<212> DNA

<213> Homo sapien

<400> 67

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cttgagaaag caggattggt ttaagttcca agatttaaca aacttactgt tcagcatcat    60
attcaagcct aaaaggaaga taggattttc aagatatatt tccaacttct ttaacatggc    120
accatggatg aactgtttct cagcactgtg ctgcttcact tggaattaaag gatgaattgg    180
gaggagacag tatgacatag gtgggtagggt tgggtgggtga ggggaaccag ttctaatagt    240
cctcaactcc actccagctg ttctgtgtcc acacgggtcca ctgagctggc ccagtccctt    300
tcactcagtg tgtcaccaaa ggcagcttca aggtcfaatg gcaagagacc acctataacc    360
tcttcacctt ctgctgcctc tttctgctgc cactgactgc catggccatc tgctatagcc    420
gcattgtcct cagtgtgtcc agggcccaga caagggaagg gagccatggt gagactccaa    480
ttcccaggcc ttaatcctta accctagacc tgttgccctc agcatcattt atttatctac    540
ctacctaaata gctatctacc agtcattaaa ccatgggtgag attctaacca tgtctagcac    600
ctgatgctag agataatttt gttgaatccc ttcaattata aacagctgag ttagctggac    660
aaggactagg gaggcaatca gtattattta ttcttgaaca ccatcaagtc tagacttggg    720
ggcttcatat ttctatcata atccctgggg gtaagaaatc atatagcccc aggttgggaa    780
ggggaaaacg gtttgcaaca ttctcctcct tgtaggaggc gagctctgtc tcactagcta    840
tgcccctcca tcaattcacc ctatactcag atcagaagct gagtgtctga attacagtat    900
attttctaaa ttctagccc ctgctggtga atttgcctc ccccgctcct ttgacaattg    960
tccccgtggt cgtctccggg cctgagact ggccctgctt atcttgcctga ccttcacct    1020
ct                                         1022

```

<210> 68

<211> 449

<212> DNA

<213> Homo sapien

<400> 68

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ccagatccat ttctagtggt ctggatttct ttttattttc ttttcaactt gaaagaaact    60
ggacattagg cactatgtg ttgttactgc cactagtgtt caagtgcctc ttgttttccc    120
agagatttcc tgggtctgcc agaggcccag acaggctcac tcaagctctt taactgaaaa    180
gcaacaagcc actccaggac aaggttcaaa atggttacaa cagcctctac ctgtcgcccc    240
agggagaaag gggtagtgat acaagtctca tagccagaga tggttttcca ctcttctag    300
atattcccaa aaaggaggctg agacaggagg ttattttcaa ttttattttg gaattaaata    360
cttttttccc ttattactg ttgtagtccc tcaattggat atacctctgt tttcacgata    420
gaaataaggg aggtctagag cttctattc                                         449

```

<210> 69

<211> 387

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(387)

<223> n = A,T,C or G

<400> 69

```

gcccttagcg tgggtcgcg cncgangtct ggagcntatg tgatncctat ggtncncagg    60
cnnatactgc tantctcatt tattctcctg cnacctantc ctctnctctg gaatcacacc    120
attattgcct gttaacactg gactgtgagt accangcaat taatttgcac caanaaagtt    180
gagggatatta tcanatattg caatctgtac agagggaaga tgatttcaat ttgatttcaa    240
cttaacccttc atctttgtct gttaacacta atagagggtg tctaataaaa tggcaaattt    300
gngatctcat tnggtataac tacactcttt ttcacagatg tgatgactga atttccanca    360
acctgcccgg gcgngcgnrc naagggc                                         387

```

<210> 70

<211> 836

<212> DNA

<213> Homo sapien

<400> 70
 tattccattt acaaaataaa ttcagccctg cactttcttt agatgccttg atttccagaa 60
 tggagcttag tgctactgaa taccctggcc acagagccac cttaggatat tcttttctcc 120
 accctagttt atttatttat agatatctgt ttacaaagtc tgtagtaaatt cctgatgctg 180
 accatctgaa atgtactttt tttctgaatg ctgtttcaat ctaaaatagc agcttttgag 240
 aaaacaatga tgtaaattcc ttatgataaa aggatgattc tatatatctt ttaatgatat 300
 taaatatgcc gaagccaagc acacagtctt tctaaagtgt gtgtatgttt gtgtgaatgt 360
 gaatgatact gatcttatat ctgtttaaag ttgtttttaa aagctgtggc atcccattgt 420
 tcatatttgc caagtcttct gtaaagatgt ctaggacgaa atattttatg tgctaattgca 480
 tgtatttgta aaccagattt gtttaccact caaaattaac ttgttttctt catccaaaaa 540
 agtttatttc ttccacgtac tttaaattttc tgtgtgggta taatatagct ttctaatttt 600
 tttctttcac aaaggcaggt tcaaaattct gttgaaagaa aaatgctttc tgaaactgag 660
 gtataacacc agagcttgct gtttaaagga ttatatgatg tacatcagtt ctataaatgt 720
 gctcagcagt ttaacatgtg aatcctgttt taaagtgtc agatttcaac tgtgtaagcc 780
 attgatataa cgctgtaatt aaaaatgttt atatgaaaaa aaaaaaaaaa aaaaaa 836

<210> 71
 <211> 618
 <212> DNA
 <213> Homo sapien

<400> 71
 gttgcagtga gctcaagtgt tgggtgtatc agctcaaaac accatgtgat gccaatcatc 60
 tccacaggag caatttgttt accttttttt tctgatgctt tactaacttc atcttttaga 120
 tttaaatcat tagtagatcc tagaggagcc agtttcagaa aatatagatt ctagtctcagc 180
 accacccgta gttgtgcatt gaaataatta tcattatgat tatgtatcag agcttctggg 240
 tttctcattc tttattcatt tattcaacaa ccacgtgaca aacactggaa ttacaggatg 300
 aagatgagat aatccgctcc ttggcagtgt tataactatta tataacctga aaaaacaaac 360
 aggtaatatt cacacaaagt aatagatatt atgacacatt taaaataggg cactactgga 420
 acacacagat aggacatcca ggttttgggt caatatgtga gactttttgg tggatgagat 480
 atgcaggttg atrccagaag gacaacaaaa acatatgtca gatagaaggg aggagcaaat 540
 gccaagagct ggagctgagg aagatcactg tgaaattcta tgtagtctag ttggctggat 600
 gctagagcaa agaggtag 618

<210> 72
 <211> 806
 <212> DNA
 <213> Homo sapien

<400> 72
 tctacgatgg ccatttgctc attgtctttc ctctgtgtgt agtgagtgaac cctggcagtg 60
 tttgctgtct cagagtggcc cctcagaaca acagggctgg ccttggaaaa accccaaaac 120
 aggactgtgg tgacaactct ggtcaggtgt gatttgacat gagggccgga ggcggttgct 180
 gacggcagga ctggagaggg tgcgtgcccc gcactggcag cgaggctcgt gtgtccccc 240
 ggcagatctg ggcactttcc caaccaggt ttatgccgtc tccagggaag cctcggtgcc 300
 agagtgggtg gcagatctga ccatccccac agaccagaaa caaggaattt ctgggattac 360
 ccagtccccc ttcaaccag ttgatgtaac cacctcattt tttacaaata cagaatctat 420
 tctactcagg ctatgggcct cgtcctcact cagttattgc gagtgttgct gtccgcattg 480
 tccgggcccc acgtggctcc tgtgctctag atcatggtga ctccccgcc ctgtggttg 540
 aatcgatgcc acggattgca ggccaaattt cagatcgtgt ttccaaacac ccttgctgtg 600
 ccttttaatt ggattgaaag cacttttacc acatggagaa atatattttt aatttgatg 660
 gcttttctac aaggtccact atttctgagt ttaatgtgtt tccaacactt aaggagactc 720
 taatgaaagc tgatgaattt tcttttctgt ccaacaagt aaaaataaaa taaaagtcta 780
 tttagatgtt gaaaaaaaaa aaaaaa 806

<210> 73
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature

18

<222> (1)...(301)

<223> n = A, T, C or G

<400> 73

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gagccattgt	caacagcaga	gatgctgttg	aaactcaatc	ccaacttagc	caaattattc	120
agtcctttca	ggctagctgc	atcaactctg	ctgattttgt	tgccatcaag	atgtaattcc	180
gtaagggaag	gaggaagacc	ttgagggaatg	ctggygatat	tggyatcagc	aatgcggtatg	240
tasgaagagc	ttcttcmttc	cctggaaagc	cccattttca	atyccttgag	ctcttcakcg	300
g						301

<210> 74

<211> 401

<212> DNA

<213> Homo sapien

<400> 74

agttttacatg	atccctgtaa	cagccatggt	ctcaaactca	gatgcttcct	ccatctgcca	60
agtgtgttct	ggatacagag	cacatcgtgg	cttctggggg	cacactcagc	ttaggctgtg	120
gggtccacaga	gcactcatct	ggctgggcta	tggtggtggt	ggctctactc	aagaagcaaa	180
gcagttacca	gcacattcaa	acagtgtatt	gaacatcttt	taaatatcaa	agtgagaaac	240
aagaaggcaa	cataataatg	ttatcagaaa	gatgttagga	agtaaggaca	gctgtgtaaa	300
gcttgaggct	gaaaagtagc	ttgccagctt	catttctttg	gtttcttggg	tagtgggccg	360
ccggaacagc	aagatgtgag	gttctggttc	atggatcata	t		401

<210> 75

<211> 612

<212> DNA

<213> Homo sapien

<400> 75

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aagagtgttg	aaaaaaaat	tcaaattttt	ggggagcgag	ggaaggagtt	aatgaaactg	120
tattgcacaa	tgctctgac	aatccttctt	tttctctttt	gcccacaatt	taagcaagta	180
gatgtgcaga	agaaatggaa	ggattcagct	ttcagttaaa	aaagaagaag	aagaaatggc	240
aaagagaaag	ttttttcaaa	tttctttctt	ttttaattta	gattgagttc	atttatttga	300
aacagactgg	gccaatgtcc	acaaagaatt	cctggtcagc	accaccgatg	tccaaagggtg	360
caatatcaag	gaagggcagg	cgtgatggct	tatttgtttt	gtattcaatg	attgtctttc	420
cccattcatt	tgtcttttta	gagcagccat	ctacaagaac	agtgtaaagt	aacctgctgt	480
tgccctcagc	aacaagttca	acatcattag	agccctgtag	aatgacagcc	tttttcaggt	540
tgccagctct	ctcatccatg	tatgcaatgc	tgttcttgca	gtggtagggtg	atgttctgag	600
aggcatagtt	gg					612

<210> 76

<211> 844

<212> DNA

<213> Homo sapien

<400> 76

ggcttttcgag	cggccgccc	ggcaggtctg	atggttctcg	taaaaacccc	gctagaaact	60
gcagagacct	gaaattctgc	catcctgaac	tcaagagtgg	agaatactgg	gttgacccta	120
accaaggatg	caaattggat	gctatcaagg	tattctgtaa	tatggaaact	ggggaaacat	180
gcataagtgc	caatcctttg	aatgtttccac	ggaaacactg	gtggacagat	tctagtgtcg	240
agaagaaaca	cgtttggttt	ggagagtcca	tggtggtgg	ttttcagttt	agctacggca	300
atcctgaact	tcttgaagat	gtccttgatg	tgacgcykcg	attccttcga	cttctctcca	360
gccgagcttc	ccagaacatc	acatatcact	gcaaaaatag	cattgcatac	atggatcagg	420
ccagtggaaa	tgtaaagaag	gccctgaagc	tgatggggtc	aatgaagggt	gaattcaagg	480
ctgaaggaaa	tagcaaattc	acctacacag	ttctggagga	tggttgacag	aaacacactg	540
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ccaccaatgt	ccagaggtgc	aatgtcaagg	aacggcaggc	gagatggctt	atttgttttg	660
tattcaatga	ttgtcttgcc	ccattcatct	gtcttttttg	agcagccatc	gactaggaca	720
gagttaggtga	acctgctggt	gccctcagca	acaagttcca	catcgttgga	accctgcaga	780

19

agcacagcct tgttcaarct gcccgctctcc tcatccagat acctcggccg cgaccacgct 840
aatc 844

<210> 77
<211> 314
<212> DNA
<213> Homo sapien

<400> 77
ccagtcctcc acttggcctg atgagagtgg ggagtggcaa gggacgtttc tcctgcaata 60
gacacttaga tttctctctt gtgggaagaa accacctgtc catccactga ctcttctaca 120
ttgatgtgga aattgctgct gctaccacca cctcctgaag aggcttccct gatgccaatg 180
ccagccatcc tggcatcctg gccctcgagc aggtcgcggt aagtagcgat ctctgctcc 240
agccgtgtct ttatgtcaag cagcatcttg tactcctggg tctgagcctc catctcgcat 300
cggagctcac tcag 314

<210> 78
<211> 548
<212> DNA
<213> Homo sapien

<400> 78
accaagagcc aagtgttaca caggatattt taaaaataaa atgttttttg aatcctcacc 60
tcccattgcta tcttctaaga taactacaaa tattcttcaa agatttaact gagttctgcc 120
aaggacctcc caggactcta tccagaatga ttattgtaaa gctttacaaa tcccaccttg 180
gccttagcga taattaggaa atcacaggca aacctcctct ctgggagacc aatgaccagg 240
ccaatcagtc tgcacattgg ttttggttaga tactttgtgg agaaaaacaa aggctcgtga 300
tagtgcagct ctgtgcctac agagagcctc ccttttggtt ctgaaattgc tgatgtgaca 360
gagacaaaagc tgctatgggt ctaaaacctt caataaagta actaatgaca ctcaagggtcc 420
tgggactctg agacagacgg tggtaaaacc cacagctgcg attcacattt ccaattttatt 480
ttgagctctt tctgaagctg ttgcttccta cctgagaatt cccatttaga gagctgcaca 540
gcacagtc 548

<210> 79
<211> 646
<212> DNA
<213> Homo sapien

<400> 79
accccgctcac tatgtgaata aaggcagcta gaaaatggac tcaattctgc aagccttcat 60
ggcaacagcc catattaaga cttctagaac aagttaaaaa aaatcttcca tttccatcca 120
tgcatgggaa aagggtctta gtatagttta ggatggatgt gtgtataata ataaaatgat 180
aagatatgca tagtggggga ataaagcctc agagtccttc cagtatgggg aatccattgt 240
atcttagaac cgagggattt gtttagattg ttgatctact aatttttttc ttcaattata 300
tttgaatttt caatgatagg acttattgga aattggggat aattctgttg tggattataa 360
taatattcat tttttaaaaa ctcattcttg tattgagtta gtgcattgac ttccaatgaa 420
ttgacataag cccatatttc attttaacca gaaacaaaaa ctagaaaatg ttactcccta 480
aataggcaac aatgtatttt ataagcactg cagagattta gtaaaaaaca tgtatagtta 540
ctttagaaac aacttctgac acttgagggt tacccaatgg tctccttccc attctttata 600
tgaggtaaat gcaaaccagg gagccaccga ataaacagcc ctgagt 646

<210> 80
<211> 276
<212> DNA
<213> Homo sapien

<220>
<221> misc feature
<222> (1)... (276)
<223> n = A,T,C or G

<400> 80

20

gtctgaatga	gcttcnctgc	gagatgganc	ancataaccc	agaantccaa	aancntanng	60
aacgnnaaaa	cccgnntngaa	caagnaaacn	gcaactnacg	gccgcctgnt	gnagggcgag	120
gacgcccacc	tctcctcctc	ccagttctcc	tctggatcgc	agncatccan	agatgtgacc	180
tcttccagcc	gccaaatccg	caccaaggtc	atggatgtgc	acgatggcaa	ggtgggtgtc	240
caccacgaa	caggtccttc	gcaccaagaa	ctgagg			276

<210> 81
 <211> 647
 <212> DNA
 <213> Homo sapien

<400> 81						
gtcctgcctt	tcctcttttc	tttaaaaaaa	ataaatgttt	acaaaacatt	tccctcagat	60
tttaaaattc	atggaagtaa	taaacagtaa	taaaatatgg	atactatgaa	aactgacaca	120
cagaaaaaca	taaccataaa	atattgttcc	aggatacaga	tattaattaa	gagtgacttc	180
gttagcaaca	cgtagacatt	catacatatc	cggtggaaga	ctggtttctg	agatgcgatt	240
gccatccaaa	cgcaaatgct	tgatcttggg	gtaggrtaat	ggccccagga	tcttgcagaa	300
gctctttatg	tcaaaacttct	caagttgatt	gacctccagg	taatagtttt	caaggttttc	360
attgacagtt	ggtatgtttt	taagcttgtt	ataggacaga	tccagctcaa	ccagggatga	420
cacattgaaa	gaatttccag	gtattccact	atcagccagt	tcgttgtgag	ataaacgcag	480
atactgcaat	gcattaaaac	gcttgaaata	ctcatcaggg	atgttgctga	tcttattgtt	540
gtctaagtag	agagttagaa	gagagacagg	gagaccagaa	ggcagtctgg	ctatctgatt	600
gaagctcaag	tcaaggtatt	cgagtgtatt	aagaccttta	aaagcag		647

<210> 82
 <211> 878
 <212> DNA
 <213> Homo sapien

<400> 82						
ccttctttcc	ccactcaatt	cttcctgccc	tgattattaat	taagatatct	tcagcttgta	60
gtcagacaca	atcagaatya	cagaaaaatc	ctgcctaagg	caaagaaata	taagacaaga	120
ctatgatatac	aatgaatgtg	ggtaaagtaa	tgattttcca	gctaaattgg	tctaaaaaag	180
aatattaagt	gtggacagac	ctattttcaa	ggagcttaat	tgatctcact	tgttttagtt	240
ctgatccagg	gagatcaccc	ctctaattat	ttctgaactt	ggttaataaa	agttttataag	300
atttttatga	agcagccact	gtatgatatt	ttaagcaaat	atgtttattta	aaatattgat	360
ccttcccttg	gaccaccttc	atgttagttg	ggtattataa	ataagagata	caaccatgaa	420
tatattatgt	ttatacaaaa	tcaatctgaa	cacaattcat	aaagatttct	cttttataacc	480
ttcctcactg	gccccctcca	cctgcccata	gtcaccaaat	tctgttttaa	atcaatgacc	540
taagatcaac	aatgaagtat	tttataaaatg	tattttatgct	gctagactgt	gggtcaaatg	600
tttccctttt	caaattattt	agaattctta	tgagttttaa	atttgtaa	ttctaaatcc	660
aatcatgtaa	aatgaaactg	ttgctccatt	ggagtagtct	cccacctaaa	tatcaagatg	720
gctatatgct	aaaaagagaa	aatatggtca	agtctaaaat	ggctaattgt	cctatgatgc	780
tattatcata	gactaatgac	atttatcttc	aaaacaccaa	attgtcttta	gaaaaattaa	840
tgtgattaca	ggtagagaac	ctcggccgcg	accacgct			878

<210> 83
 <211> 645
 <212> DNA
 <213> Homo sapien

<400> 83						
acaaacattt	tacaaaaaag	aacattacca	atatcagtgg	cagtaagggc	aagctgaaga	60
ataaatagac	tgagtttccg	ggcaatgtct	gtcctcaaag	acatccaaac	tgctttcagg	120
cagctgaaac	aggcttcttt	cccagtgaca	agcatatgtg	gtcagtaata	caaacgatgg	180
taaatgaggc	tactacatag	gcccagttaa	caaactcctc	ttctcctcgg	gtaggccatg	240
atacaagtgg	aactcatcaa	ataatttaaa	cccaaggcga	taacaacgct	atttcccatc	300
taaaactcatt	taagccttca	caatgtcgca	atggattcag	ttacttgcaa	acgatcccg	360
gttgctacac	agatacttgt	ttttacacat	aacgctgtgc	catcccttcc	ttcactgccc	420
cagtcagggtt	tctgtgtgtt	ggaccgaaag	gggatacatt	ttagaaatgc	ttccctcaag	480
acagaagtga	gaaagaaagg	agaccctgag	gccaggatct	attaaacctg	gtgtgtgcgc	540
aaaaggagg	gggaaggcag	gaatttgaaa	ggataaacgt	ctccttttgc	ccgaggaatc	600

aggaagcgtg actcacttgg gtctgggacg ataccgaaat ccggt 645

<210> 84
 <211> 301
 <212> DNA
 <213> Homo sapien
 <220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 84
 tctgatgtca atcacaaactt gaaggatgcc aatgatgtac caatccaatg tgaaatctct 60
 cctcttatct cctatgctgg agaaggatta gaaggttatg tggcagataa agaattccat 120
 gcacctctaa tcatcgatga gaatggagtt catgggctgg tgaaaaatgg tatttgaacc 180
 agataccaag ttttgtttgc cacgatagga atagctttta tttttgatag accaactgtg 240
 aacctacaag acgtcttggg caactgaagn ttaaatatcc acanggggtt attttgcttg 300
 g 301

<210> 85
 <211> 296
 <212> DNA
 <213> Homo sapien
 <220>
 <221> misc_feature
 <222> (1)...(296)
 <223> n = A,T,C or G

<400> 85
 agcgtgggtc gcggnccgan gtagagaacc gactgaaacg tttgagatga agaaagtctt 60
 cctoctgac acagccatct tggcagtggc tgttggtttc ccagtctctc aagaccagga 120
 acgagaaaaa agaagtatca gtgacagcga tgaattagct tcagggtttt ttgtgttccc 180
 ttacccatat ccatttcgcc cacttccacc aattccattt ccaagatttc catggtttan 240
 acgtaatttt cctattccaa tacctgaatc tgccccata actccccttc ctagec 296

<210> 86
 <211> 806
 <212> DNA
 <213> Homo sapien

<400> 86
 tctacgatgg ccatttgcct attgtctttc ctctgtgtgt agtgagtgc cctggcagtg 60
 tttgcctgct cagagtggcc cctcagaaca acagggctgg ccttggaata accccaaaac 120
 aggactgtgg tgacaactct ggtcagggtg gatttgacat gagggccgga ggcggttgct 180
 gacggcagga ctggagaggc tgcgtgcccg gcactggcag cgaggctcgt gtgtcccca 240
 ggcagatctg ggcactttcc caaccaggt ttatgccgtc tccagggaag cctcggtgcc 300
 agagtgggtg gcagatctga ccatccccc acaccagaaa caaggaattt ctgggattac 360
 ccagtcccc ttcaaccag ttgatgtaac cacctcattt tttacaaata cagaatctat 420
 tctactcagg ctatgggcct cgtcctcact cagttattgc gagtgttgct gtccgcagtc 480
 tccgggcccc acgtggctcc tgtgctctag atcatggtga ctccccgcc ctgtggttgg 540
 aatcgatgcc acggattgca ggccaaattt cagatcgtgt ttccaaacac ccttgctgtg 600
 ccctttaatg ggattgaaag cacttttacc acatggagaa atatattttt aatttgatgat 660
 gcttttctac aaggtccact atttctgagt ttaatgtgtt tccaacactt aaggagactc 720
 taatgaaagc tgatgaattt tcttttctgt ccaacaagt aaaataaaaa taaaagtcta 780
 tttagatgtt gaaaaaaaa aaaaaa 806

<210> 87
 <211> 620
 <212> DNA
 <213> Homo sapien

```

<400> 87
tttttgcac agatctgaaa tgtctgagag taatagtctt tgttgaattt tttttgttc      60
atttttctgc acagtccatt ctgtttttat tactatctag gcttgaaata tatagtttga      120
aattatgaca tccttcctct ttgttatttt cctcatgatt gctttggcta ttcaaagttt      180
attttagttt catgtaaatt tttgaattgt attttccatt attgtgaaaa tagtaccact      240
gcaattttaa taggaagttt attgaatcta tagattactt tggataatat ggcacttcaa      300
taataattcat gttttcaatt catagacaaa atattttaaa atttatttgt atcttttcta      360
atttttcctt tttttattgt aaagattttac ctccctgggt aatattttcc tcagaaattt      420
attatttaag gtatagtcaa taaaattttc ttccctctatt ttgtcagata gtttaagtgt      480
atgaaacat agatatactt gtatgttaat tttatatttt gctaattttac tgagtgtatt      540
tattagttaa gagaggtttt aatgtactgt ttatggtttt ttaaataata gattacttat      600
tttttaaaaa aaaaaaaaaa

```

```

<210> 88
<211> 308
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(308)
<223> n = A,T,C or G

```

```

<400> 88
tagctgtgnt cagcaggccg aggttttttt tttttttgag atggagtctc gccctgtcac      60
ccaggctgga gtgcagtggc ctgatctcag ctcaactgcaa gctccacctc ctggattcac      120
gctattctcc tgcctcagcc tcccaagtag ctgggactac aggcgcccgc caccacgccc      180
agctaattnt ttgnattttt agtacnagat gcggtttcat cgtgttagcc agcatggnc      240
cgatctcctg acctcgtgaa ctgcccgcct cggcctccca aagacctgcc cgggcnggcc      300
gctcgaaa

```

```

<210> 89
<211> 492
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(492)
<223> n = A,T,C or G

```

```

<400> 89
agcggccgcc cgggcaggtc tgtaagtaa catacatatc accttaataa aaatcaagat      60
gaaatgtttt agaaactatt ttatcaaaag tggctctgat acaaagactt gtacatgatt      120
gttcacagca gcactattaa tgccaaaaag tagacaaaac ctaaagtgtc attaactgat      180
aagcaaaatg tggatatatc atacaatgga atattatgta gcccaacaac tggcatggag      240
tactacaaca tggatgagcc tcaaaaacgt tatgctaaat gaaaaaagtc agatatagga      300
aaccacatgt catatgatcc catttatatg aaatagccag aaaaggcaag tcatagaaac      360
aagatagatc ggaaaatggg ttggaggact acaaattggc ccagggatct ttgaagttga      420
tggaatgggt ctaaaatcag actgtggntg tggttgaaca agtctgtaaa tttaccaaaa      480
tgcgttaata ca

```

```

<210> 90
<211> 390
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(390)
<223> n = A,T,C or G

```

```

<400> 90
tcgagcggcc gcccgggcag gtacaagcgt tttttttttt tttttttttt ttttctaaca    60
gttctctgtt ttattgcaat acagcaaagt ctggttaata ttaagngata tcaacataaa    120
gtattggtga ggagtccttt gtgacatttt ttaccatccc accttaaata tttctgtgca    180
aaanaatcca catcattggt tggtancaaa ggatctctta aaaagttccc taanacactg    240
agggcataaa accaaacaaa ataaaataag gagtgatagg ctaaagcagt atcttcccct    300
ccatccacat ttgncaagca ttatatctta accaaaaaat gatcacacca ggccatgcaa    360
aactgtccaa tattaccgag aaaaaaccct

```

```

<210> 91
<211> 192
<212> DNA
<213> Homo sapien

```

```

<400> 91
agcgtggtcg cggccgaggt ctgtcaatta atgctagtc tcaggattta aaaaataatc    60
ttaactcaa gtccaatgca aaaacattaa gttggttaatt actcttgatc ttgaattact    120
tccgttacga aagtccttca catttttcaa actaagctac tatatttaag gcctgcccg    180
gcggccgctc ga

```

```

<210> 92
<211> 570
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(570)
<223> n = A,T,C or G

```

```

<400> 92
agcgtggtcg cggccgaggt ctgacaacta acaaagaagc aaaaactggc atcttggaca    60
tcctagtatt acacttgcaa gcaattagaa cacaaggagg gccaggaaa aagtttagct    120
ttgaatcaact tccaaatcta ctgattttga gggtccgcag tagttctaac aaaacttttc    180
agacaatggt aactttcgat taagaaagaa aaaaacccca aacatcttca ggaattccat    240
gccaggttca gtctcttoca gtgagcccgcc ttgctaaaag tccacgtgca ccattaatta    300
gctgggctgg cagcaccatg taaaaagaag cctattcacc accaaccaca cagactagac    360
atgtaaagta ggatcaagta atggatgaca accatggtcg tggaatatgg tcaatgagag    420
tcagaaaagt acaggcacca gtacaagcag cagataacag aattgacggg ccaaaggata    480
aaaataggct tatttaataa ggatgctaca gaacacatnc acttctaatt ggaagctgct    540
ttacactggg tggcattgna ccatatgcat

```

```

<210> 93
<211> 446
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(446)
<223> n = A,T,C or G

```

```

<400> 93
tcgagcggcc gcccgggcag gtccagggtt ttatttagtt gtgtaatctt ggacaagtta    60
cctaactttt ttgagtctga atatatatta tctgcaaaat gagaatcatg ataatacgtc    120
ataggcttaa ttaggaggat taaatgaaat aatttatagg tggtgccatg gttacatata    180
agtattagta gttaattctt ttocctttgt tacttttata gtataggttg gatgaaggtt    240
ccagtatagg caaaaatact acttgggggt aaagtagagt gtgatacttt atttgaaatg    300
ttocctgaat ctgatcttta ctttttgnta ctgctgcact acccaaatcc aaattttcat    360
cccaacattc ttggatttgt gggacagcng tagcagcttt tccaatataa tctatactac    420
atcttttctt actttggtgc tttttg

```


<210> 94
 <211> 409
 <212> DNA
 <213> Homo sapien

<400> 94
 cgagcgccg cccgggcagg tccatcagct cttctgctta gaatacgagg cagacagtgg 60
 agaggtcaca tcagttatcg tctatcaggg tgatgaccca agaaaggtag gtgagaagggt 120
 gtcggcacac acgcctctgg atccacccat gcgagaagcc ctcaagttgc gtatccagga 180
 ggagattgca aagcgccaga gccaacactg accatgttga aggcgttctc tccaggctgg 240
 attcactgca ctcggaagaa ttctgcccag ggaatttagt gtgggggtac caggaccagt 300
 ttgtcttgat cttgagaccc ccagagctgc tgcattccata ggggtgttga ggactacacc 360
 tggcctgcct tgcagtcatt ctttcttata tgttgaccca tttgcccac 409

<210> 95
 <211> 490
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(490)
 <223> n = A,T,C or G

<400> 95
 tcgagcgccc gcccgggcag gtccactctg tttgcagctt ccacacactg cacctaccta 60
 ctacctctct tccatgctta actgggttta gaaaggtag ctatgcgtag aagaactact 120
 tgggatattc aagtgcctga tttgaacgat aagcctatag ataacagtct gaagctgcaa 180
 gggagacttt gttagtacac tactataaac aggtaaacta cctgttttga cttgatatag 240
 tgcataatgaa atgactgatt taatacaaaa ctacagaaca tgcaaaattt tttctgagat 300
 gttaaagtatt acttcagtgg agaacaaaac ttacttaacc tttcgctaat gcatgtagta 360
 ccagaaaagca aacatgggtt tagcttcctt tactcaaaat atgaacatta agtgggtgtg 420
 aattttgtct gccaaagtgt tcagaaaata cattataaat aacctaagtt aaaaaaaga 480
 aactgngaac 490

<210> 96
 <211> 223
 <212> DNA
 <213> Homo sapien

<400> 96
 agcgtggtcg cggccgaggt ctggaagccc accctaggac ttgaatggca ccttgtcctt 60
 tctctgccag taatgcaatc caacacaata tgctacaggg aaaacagaat ttccacgggtg 120
 ccgccctctg gtacaaggga aacagcacgc aaagcaaaaag gccacagagg gctccctgag 180
 aatccagtac aactaagcga ggacctgccc ggcggccgc tcg 223

<210> 97
 <211> 527
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(527)
 <223> n = A,T,C or G

<400> 97
 tcgagcgccc gcccgggcag gtctgtgcag gagacactga agtgggtagt gtccataatc 60
 tttttagcct gttgctgaaa ttccagtgtg actccttcaa accaaaatgc ttacaggatc 120
 atgggaaagc ctcggttgca gaaatcaaga caggcaagtg ggaagataac tcggcttttga 180
 gggttaaacag atctgggttc aaagcatagt ttcactctct gtcttgtgaa gtgtcctggg 240

tgaagtcatt	tcctctcttg	aatttcagag	aggatgaaaa	tataaaaagt	ataataacta	300
tcttcataat	ctttgtgagg	attaaagaag	acgaagtgtg	tgaaaagcta	agcacagagc	360
aggcattcta	caataagtag	ttattatttt	tggaaccatc	ccgnccttag	ccccagcca	420
attaccttct	cttagnctct	tcatatcgaa	ngccgtaatc	ttgaccttct	cttgcnactg	480
gattgggtgct	ggttgatgcc	caaaacttccc	gagatgctgt	ctgggaa		527

<210> 98

<211> 514

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(514)

<223> n = A,T,C or G

<400> 98

tcgagcggcc	gcccgggcag	gtctggctcc	catggccctt	ggggtggcct	gactctgtca	60
ctatttcctaa	aaccttctag	gacatctgct	ccagggaagaa	ctttcaacac	caaaattcat	120
ctcaatttta	cagatgggaa	aagtgattct	gagaccagac	cagggtcagg	ccaaggtcat	180
ccagcatcag	tggctgggct	gagactgggc	ccagggaacc	ctgtctgctc	ctctttttcc	240
cagagctgtg	agttctctag	ccaaggctgc	actcttgagg	gagagccagg	aagcatagct	300
gaggccatga	caacctcact	cttcacctga	aaattttaacc	cgtggcagag	gatccaggca	360
catataggct	tcggagccaa	acaggacctc	ggcgcgacc	acgctaagcc	gaattccagc	420
acactggcgg	ccgttactag	tggatcccga	gcttnggtac	caagcttggc	gtaatcatgg	480
gcatagctgg	ttcctggggg	gaaaatggta	tccg			514

<210> 99

<211> 530

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(530)

<223> n = A,T,C or G

<400> 99

tcgagcggcc	gcccgggcag	gtctgaagaa	acagggtataa	atttggcagc	cagtaatttt	60
gacaggggaag	ttacagcttg	catgacttta	aatatgtaaa	tttgaaaata	ctgaatttcg	120
agtaatcatt	gtgctttgtg	ttgatctgaa	aaatataaca	ctggctgtcg	aagaagcatg	180
ttcaaaaata	tttaattcac	ttcaaaatgt	catacaaaat	atgggtgggtt	ctatgcaccc	240
ctaaagcttc	aagtcattta	gctcagggtac	atactaaagt	aatatattaa	ttcttccagt	300
acagtgggtgt	ttcataccat	tgacatttgc	ataccctaga	ataattttaag	aaagacatgt	360
gtaatatcca	caatgttcag	aaaagcaagc	aaaaggtcaa	ggaacctgct	ttggttcttc	420
tggagatggn	ctcatatcag	cttcataaac	attcattcta	caaaatagta	agctaaccat	480
ttgaaccca	atttccagat	taagcatatt	ttctcataaa	tnatgaagcc		530

<210> 100

<211> 529

<212> DNA

<213> Homo sapien

<400> 100

agcgtggctg	cggccgaggt	ccaggcacgg	tggcttatgt	gtgtaatccc	agcacttggg	60
gaggctgagg	gagggtggatc	acttgagtcc	aggagtttga	gaccagtctg	ggcaacatgg	120
cgaaacttca	tcactacca	agaagaaaa	aattagccag	gtgtgggtgg	gtatgcctgt	180
agtcccagat	actctgggtg	ctgagggtgag	aggatagctt	gagcccagga	aattgaggct	240
gcagtgaact	atgattgcac	tactgtgctc	cagcttgggc	aacagagtga	gatcttgtct	300
ccaaaagtcc	ttgaaggatt	ttaggaagtt	gttaaaagtc	ttgaaacgat	gtttgggggc	360
atggttaggg	tcttgaatgt	ttaattcctc	taataactgc	ttattcaaga	gaagcatttc	420
tgactgggtg	cggggcagtg	gcttcatgcc	ccataatccc	agtacttttg	gaggctgaag	480

caggaacatt gcttgagccc aggacttcaa gaacagcctg ggtaacata 529

<210> 101
<211> 277
<212> DNA
<213> Homo sapien

<400> 101
tcgagcggcc gcccgggcag gtcgcaggaa gaggatggaa actgaggagt ccaggaagaa 60
gagggaaacga gatcttgagc tggaaatggg agatgattat attttggatc ttcagaagta 120
ctgggattta atgaatttgt ctgaaaaaca tgataagata ccagaaatct ggggaaggcca 180
taatatagct gattatattg atccagccat catgaagaaa ttggaagaat tagaaaaaga 240
agaagagctg agaacagacc tcggccgcga ccacgct 277

<210> 102
<211> 490
<212> DNA
<213> Homo sapien

<400> 102
gcgtggtcgc gcccgaggtc tgacggcttt gctgtcccag agccgcctaa acgcaagaaa 60
agtcgatggg acagtttagag gggatgtgct aaagcgtgaa atcagttgtc cttaattttt 120
agaaagattt tggtaactag gtgtctcagg gctgggttgg ggtccaaagt gtaaggaccc 180
cctgccttta ttggagagct ggagcttgga gacattacc cttcatcaga aggaattttc 240
ggatgttttc ttgggaagct gttttgggtcc ttggaagcag tgagagctgg gaagcttctt 300
ttggctctag gtgagttgtc atgtgggtaa gttgaggtta tcttgggata aagggtcttc 360
tagggcacia aactcactct aggtttatat gtatgtagc ttatatattt tactaagggtg 420
tcaccttata agcatctata aattgacttc tttttcttag ttgtatgacc tgccccgggc 480
ggccgctoga 490

<210> 103
<211> 490
<212> DNA
<213> Homo sapien

<400> 103
gagcggcgc ccgggcaggt ccaaaccagc ttgtcataa gtcattaacc aaatccatta 60
taggtaattt gttcagttca atgtttacaa ttcttatgga aaaaattagc aacacacaca 120
tttaaacgt gtgcatttac ctttgcgtga gtgcttaaaa tacatatctt tatttcaaga 180
tgacatttaa aaattattct aatatatcag cagcaaaaaat ataatttgca attacaaaaa 240
actaaactag aatccttaag ttattctcat gtttacagt gtgattcttt aataaatact 300
attatgcagc tctattgttt aagctttctg gatttggttt aaacacatgc atatatattg 360
tcaattgtgg gaagctttac aagttatatt ccatgcactt tttggacaga gttctaacag 420
agccagccag tccacaaaac aggcaagaca aaagttgaat taactggggc aaaataggac 480
tcttatgcaa 490

<210> 104
<211> 489
<212> DNA
<213> Homo sapien

<400> 104
cgtggtcgc gccgaggtcc aggtgtgtct cgaactcctg acctgtgat ctgcccgcct 60
cggcctccca aagtgttggg attacaggca tgagccactg cgcccgaccg agttgaacat 120
ttaatgtcag actaggccag agtttctcaa tctttttatt ctcacttccc aaaggagccg 180
ttggagattt tcccctcaat ctctctcctt catgaaattt cataccacaa atatagtatg 240
ttttatttat gtactgtgac ctttgaagg atcacaaacc aatataatag tttttctttt 300
taaccogtca aggaccaagt ttttgccct gttggaatg cataaactgg actgatgaat 360
tggtatagat ggctttttatc atgaggatca gaaaaacttg aaattccttg gctacgacac 420
tccatattta tcaccgtata gggaggacct tgggtatggg aagtagaaac acttctacac 480
tttacaga 489

27

<210> 105
 <211> 479
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(479)
 <223> n = A,T,C or G

<400> 105
 gcgtggcgcc gccgaggctc tgactggctt cagccccaga agttgagctg gccttttagac 60
 aaaataattg cacctccctc tgctgcttat tcccttccgt ttttcatttg agtgtgaaca 120
 gttagataaa atctgtggct gnetcttcca ccttgctcta gtttccattg ctgtgagcag 180
 gccctcctat gccccgcatt tagctacaat gctgtggact cacttgattc tttttctccg 240
 agctttgtct agaaatatgt gaaggtaggg ttaagtgcct ctctgtgtag atccacttag 300
 ccctgtctgc tgtctcgatg ggcgttgctt cgtctctcct ctcttccatc ctttccattt 360
 gcttctcacc accttctggc ttcttttctt aatgcaataa aggcagtttc taacaaagaa 420
 agaatgtggg ctttggaagt agacagacct ggnnttaaat tctgcttctg gctctccaa 479

<210> 106
 <211> 511
 <212> DNA
 <213> Homo sapien

<400> 106
 tcgcgcccca ggtccaaaac gtggattcca atgacctgcc ttgagccgc ggttgccagg 60
 agttggacct gcagtagtat gggaagctca cggcctaaat accgactgcc ctctgacccc 120
 accgtccagc gattctagaa catttctagt aggaagaca tagcaaggga ttttcatgat 180
 tgggaaatac tgggagacaa gctgaagatt tgtaagggc tatgcttctg tcatctttta 240
 ggtatttaag gctactcctt tagctagcta ctttgagctg tttaaagtga ctatctccct 300
 acacagagtt acacaatgag catctctgaa agagaatatt accctggatt tccaaagatg 360
 tactctaaca ggaagaccag gcaaaagggt acccggggga ggagtctgtt ataacactcg 420
 gaccacatg ttctcaaggc acttcagaac tttgggaaat cattttgtac cggatcctca 480
 gaaagcattt atggaaatac acatccttta g 511

<210> 107
 <211> 451
 <212> DNA
 <213> Homo sapien

<400> 107
 ggccgcgccg gcaggtccag aatatcaaat caaaagggtca caaatgttca cttcctcctc 60
 caccctctta catattggat cttcaattgc aatagggagt gtaagatggg catttttagag 120
 acgtagtgtc atcagcagaa gcaaaccat cttatacaaa tgggttttgg ggataggaaa 180
 aggctgctaa aaattcacia gtcaccattc cccagaagca atgaatagcc gtagaagacc 240
 aaggaagatc aacaagtttc caaagtgcta aagccagaga tttggccctt ccaaaatacc 300
 accaggacgc ctggagcccg gggctctccg catgtcacca ctgactgcca ggatgctgct 360
 gcacctccct tccttgagac acaacagaga gacagtgaag tcaccaaga ctgggatcat 420
 cagaggctcc tcatgcttgc tacagagaag c 451

<210> 108
 <211> 461
 <212> DNA
 <213> Homo sapien

<400> 108
 ccgccccggc aggtcctgaa aacattcaga ctaatcaaaa tgggtactact gtaacttctt 60
 ataatacata atataaaagt ttttgaaaga tatagacaca attaaccctt aaacaacaca 120
 ctatctgatt ctcaaaagca atggctatct aacaagatgt aaaaggacaa taacatatca 180
 aagaactttc acacacctaa agatagcatt tagcagcaag ttagtcagac aaaacaaaca 240
 caaatatctt cacatttcct atgtttgttt ttaactttac ttcataaaagc cactgataat 300

28

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tgaggtttct ttcaagtata agattttctaa aattaaacac tgtttttgac atatttttat 360
aaagaaataa aaagcaaac gcaatccaac tatttatatg agtccctctt ctccaacagc 420
tttagatggt tttctgagta cttttttaca cagaatattt t 461

```

```

<210> 109
<211> 441
<212> DNA
<213> Homo sapien

```

```

<400> 109
ggccgcccgg gcaggctctga ttataagaga aagaaatcca gtgacacgag ggcaggcagg 60
ccccgctctg ctctgatcga gaaaagcttc ctgatgtcag ggagatggaa ctgccaccat 120
cagaaccatg gcactttggg tgaaggtgtg tcagcgacca agggggcagg aaatgggcag 180
tgactaaggg ggcaggaaac aggcaggcac atggcaaggt tctcccagcc catcagccca 240
gtgatggcct cgattttgaa gctgcaactac tgtctgaaaa gcacaattac tgggtgactct 300
taacaaactt cagcatactg gggaaaggaga ctgtcaagta actgaattgg aaagatgaaa 360
aagaaccatc tctaaaagtt gatgcttgtc agaagaataa cctcctttgt gcaagtcttg 420
caacatcttc attcaaccac a 441

```

```

<210> 110
<211> 451
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(451)
<223> n = A,T,C or G

```

```

<400> 110
ggtcgcggcc gaggtctggg gaaggggtga gaatccctgg gccttgccca gtcctgagct 60
ctgggtgtct gcagggaagc acagtgtgta gttagtgtta aagaaagcat ccagagaggt 120
aagaggggct tgggtagcac cctttgcctc tgtcacttcc gcaaaaaactt cttgttgagg 180
aggaagatga gaaggttgac attgactttg gccttggtga agagtttcat gacagccaca 240
ccctcactact ggagctgcan gagatcctga tagtgaagct tgaaatcgct ccattgtccac 300
acccaggaac ttggcattta cttcaaaactt tcctgcctca tctcccgccg tgatgtcaaa 360
natgacgttt cttgaagtga gaggcgggaa agatcttcaa tttccaccaa agacaccctt 420
tttcaggaa gcttgagcaa caagtgtaat g 451

```

```

<210> 111
<211> 407
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(407)
<223> n = A,T,C or G

```

```

<400> 111
ggccgacgtt cgacctgact tctttngagc agntgncact acccgtcttg aggaatgccg 60
actgcagaca gtggcccang gcaaagagtg tgcgtcatcg atganattgg naagatggag 120
ctcttcagtc agntttttcat tcaagctgnt cgtcagacgc tgtctacccc agggactata 180
atcctnngca caatcccagt tcctanagga aagccactgn ctctttaga agaaatcana 240
cacanaaagg atgtgaacng tgtttaatgt caccaaggga aaacatgaaa ccaccttctg 300
ccagatatcg ggacgttgcg tgcagatcaa gcacgnaagt gaagacgcgt gcattccttg 360
ccttccgtga acgantgccc agntcaagaa gancctgatg gaaccct 407

```

```

<210> 112
<211> 401
<212> DNA
<213> Homo sapien

```

29

<220>
 <221> misc_feature
 <222> (1)...(401)
 <223> n = A,T,C or G

<400> 112
 tcgcggccga ggtcggccga ggtctgacat ctgttgctctg tgataaccac ttctgtattg 60
 cgtcttaacc acttctgtat tgtgtggttt taactgccta aggcggcaat gggcagtggg 120
 cccctttccc ttaggatggg tatcaattca acaatatatta taaggcattt actgtgtgct 180
 aagcatttgg aagacccagg ctacaaaata agacatagtt cctgccctcc aggccagcag 240
 agggaggcac aaatacccag gaatctctga tgggtgtgaa gtgcggctgt gggccacaga 300
 aaatgaccgt catggagacc ctgctaaagg tcggaccctg agcccaaagg ggtattcaga 360
 agnggagatg attttggccc cactcataga tgggtggcaa a 401

<210> 113
 <211> 451
 <212> DNA
 <213> Homo sapien

<400> 113
 gtcgcggccg aggtccatat taaaaagtcc atcataaaca aagactcctc ctcatggtat 60
 gaatatgtct catatgcccc taatgggtgca taacggactt agaaattcca atgagtctta 120
 gggttgaaat ttccaatgac ctgagcaagg cagctcccta tagcttctgg ataacatttt 180
 acaccagag ttcaggctta aacagacctt tcaacacaaat tattttcggg ttgtctgtct 240
 agaaaacggc aatgtctaaa ggaatataaa taagggtggg gggacatatg cttccagcct 300
 ggccttttct catgtggtaa aaaacaatgg aatggctgtg ttaatttttt tttaatcttt 360
 tctgaccttt actatgtttg gtaatggaaa taagtcaggg aaaacaaaat gaacaggtct 420
 catcacttaa ttaatactgg gttttcttct t 451

<210> 114
 <211> 441
 <212> DNA
 <213> Homo sapien

<400> 114
 ggcgcggccg gcaggtccat cctgtcagag atggggagaag tcacagacgg aatgatggat 60
 acaaagatgg ttacttttct tacacactat gctgacaaga ttgaatctgt tcatttttca 120
 gaccagttct ctggtccaaa aattatgcaa gaggaagggtc agcctttaaa gctacctgac 180
 actaagagga cactgttggt tacatttaat gtgcctggct caggtaacac ttacccaaa 240
 gatatggagg cactgctacc cctgatgaac atgggtgattt attctattga taaagccaaa 300
 aagttccgac tcaacagaga aggcaacaa aaagcagata agaaccgtgc ccgagtagaa 360
 gagaacttct tgaaacttga cacatgtgca aagacaggaa gcagcacagt ctcggcgagg 420
 ggaagaaaaa aagaacagag a 441

<210> 115
 <211> 431
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(431)
 <223> n = A,T,C or G

<400> 115
 gccgcggcgg caggtccatt ggcggtgaca aaaggaaaag aagcaaagag actcagtcca 60
 taatgctgat tagttagaag aaagggtctag gattgagaaa gtaccaggaa cttttaatta 120
 tttaaaagag aatgtgact gttaatgttt taaatcttac tgttcaaagt tactaatatg 180
 aatttttacc ctttgtgcat gaatattcta aacaactaga agacctccac aatttagcag 240
 ttatgaaagt taaacttttt attataaaaa ttctaaacct tactgtcctt ttaccaggaa 300
 catgacacac tatttancat cagttgcata cctcgccaat agtataattc aactgtcttg 360

cccgaaacat catctccatc tggaagacgt aagccttttag aaacacattt ttctattaat 420
 ttctctagaa c 431

<210> 116
 <211> 421
 <212> DNA
 <213> Homo sapien

<400> 116
 gtgcgcggccg aggtccagaa atgaagaaga agtttgcaga tgtattttgca aagaagacga 60
 aggcagagtgt gtgtcaaatac tttagacggca cagatgcctg tgtgactccg gttctgactt 120
 ttgaggagggt tgttcatcat gatcacaaca aggaaccggg gctcgtttat caccagtgtgag 180
 gagcaggacgt tgagcccccg ccctgcacct ctgctgttaa acacccacgc catcccttct 240
 ttcaaaagggt atccttttcat aggagaacac actgaggaga tacttgaaga atttggtattc 300
 agcccgcgaa gagattttatc aagcttaact cagataaaat cattgaaagt aataaggtaa 360
 aagctaagtc tctaacttcc aggccacgg ctcaagttaa tttcgaatac tgcatttaca 420
 g 421

<210> 117
 <211> 489
 <212> DNA
 <213> Homo sapien

<400> 117
 agcgtggtcgt cggccgaggt aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 60
 gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacagcggag accctgttaa 120
 ctactacgtt gacactgtctg tgcgccacgt gttgctcaga caggggtgtgc tgggcatcaa 180
 ggtgaagatc atgctgcctt gggacccaac tggttaagatt ggcctaaga agcccctgcc 240
 tgaccacgtg agcattgtgg aaccctaaaga tgagatactg cccaccaccc ccatctcaga 300
 acagaagggtt gggaagccag agccgcctgc catgccccag ccagtcccca cagcataaca 360
 gggctctcctt ggcagacctg cccgggcggc cgctcgaaag cccgaattcc agcacactgg 420
 cggccgttac tagtggatcc cagctcggta ccaagcttgg cgtaatcatg gtcatagtctg 480
 gtttctctgt 489

<210> 118
 <211> 489
 <212> DNA
 <213> Homo sapien

<400> 118
 tcgagcggcc gcccgggcag gtattgaata cagcaaaatt ctatatacaa agtgacctgg 60
 acctgctgct tcaaaacatg atccttttctt actaatatct tgatagtcgg tccatagagc 120
 attagaaagc aattgactct taaataaaca gaaaagtgcc taatgcacat taaatgaatg 180
 gcctaactac tggaacttta gtagttctat aagggtgatta acataggtag gatccagttc 240
 ctatgacagg ctgctgaaga acagatatga gcatcaagag gccattttgt gcaactgccac 300
 cgtgatgccca tcgtgtttct ggatcataat gttcccatta tctgattcta gacacaccac 360
 aggaatatca gtggggtcag aggttagctt agctgcttgc tgggctagaa cagatatcac 420
 tccagcatgc tcatctgaca gggccccgcg gcaaccacga ttaagtcctt gtgaatctgt 480
 gcacaggga 489

<210> 119
 <211> 181
 <212> DNA
 <213> Homo sapien

<400> 119
 taggttccag agacttttgg cccaggagga atatttactt ttagctctgg acatcattac 60
 aaaaagggaat atttccaaa cctcttcaga ccgagaatac atgggtaaaa ttattaaata 120
 gttgtataat aaaaataatt ttttccctaa aaaaaaaaaa aacctcggtc gcgaccacgc 180
 t 181

<210> 120

31

<211> 489
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(489)
 <223> n = A,T,C or G

<400> 120
 gcgtggctgc ggccgaggtc catttaaaac aaagaaaaat actaaagcca ctagtaaaaca 60
 tctgatgtgc aaaatacaac atcctctagt tggctttatg ccattattac ataagctcca 120
 aatagctcat cttaaattaa aaagaaaaag tggctgtccc atctctgctg cataaatcag 180
 attttttttt aaaggtttag agtactttta ggaagggaag ttcaaaactg ccagtgaat 240
 tcacagagaa tacaaattta gcaatttaat ttcccaaagc tctttgaaga agcaagagag 300
 tctctcttct taatgcagtg ttctcccaag aggaactgta attttgcttg gtacttatgc 360
 tgggagatat gcaaaatgtg tttttcaatg tttgctagaa tataatggtt cctcttcagt 420
 gnctggttca tcctggaact catgggttaa gaaggacttc ttggagccga actgcccggt 480
 cgggccntt 489

<210> 121
 <211> 531
 <212> DNA
 <213> Homo sapien

<400> 121
 cgagcggcgc cccgggcagg tggccagcgc tgggtccgca gacgccgaga tggaggaaat 60
 atttgatgat gcgtcacctg gaaagcaaaa ggaaatccaa gaaccagatc ctacctatga 120
 agaaaaaatg caaactgacc gggcaaatag attcgagtat ttattaaagc agacagaact 180
 ttttgacatc ttcatccaac ctgctgctca gaagactcca acttcacctt tgaagatgaa 240
 accagggcgc ccacgaataa aaaaagatga gaagcagaac ttactatccg ttggcgatta 300
 ccgacaccgt agaacagagc aagaggagga tgaagagcta ttaacagaaa gctccaaagc 360
 aaccaatgtt tgcaactgat ttgaagactc tccatcgtat gtaaaatggg gtaaaactgag 420
 agattatcag gtcccagga ttaaaactggc tcatttcttt gtatgagaat ggcataatg 480
 gtatccttgc agatgaaatg ggcctaggaa agactcttca acaatttctc t 531

<210> 122
 <211> 174
 <212> DNA
 <213> Homo sapien

<400> 122
 tcgagcggcc gcccgggcag gtctgccaac agcagaggcg ggcctccggt catcttcaaa 60
 gcacctctga gcaggtctca gccctctggc tgccggagggt gtctgggggtc tcctctgagc 120
 tcggcagcaa agcagatggt atttctctcc cgcgacctcg gccgcgacca cgct 174

<210> 123
 <211> 531
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(531)
 <223> n = A,T,C or G

<400> 123
 agcgtggtcg cggccgaggt cctcaaccaa gaggggtgat ggcctccagt caagaaactg 60
 tggctcatgc cagcagagct ctctcctcgt ccagcaggcg ccatgcaagg gcaggctaaa 120
 agacctcag tgcatacaaa tccatctagc anagagaaaa ggggcaactga agcagctatg 180
 tctgccagggt gctagggggt cctttgcaga cagcaatgct acaataaagg acacagaaat 240
 ggggggaggtg ggggaagccc tatttttata acaaagtcaa acagatctgt gccgttcatt 300


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ccccagaca cacaagtaga aaaaaaccaa tgcttggtgt ttctgccaag atggaatatt 360
cctccttcct aanttccaca catggccggt tgcaatgctc gacagcattg cactgggctg 420
cttgctctctg tggctctgggc accagtagct tgggccccat atacacttct cagttcccac 480
anggcttatg gccnangggc angctccaat tttcaagcac cacgaaggaa g 531

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```

<210> 124
<211> 416
<212> DNA
<213> Homo sapien

```

```

<400> 124
tcgagcggcc gcccgggcag gtccatctat acttttctaga gcagtaaato tcataaattc 60
acttaccaag cccaggaata atgactttta aagccttgaa tatcaactaa gacaaattat 120
gccaattctg atttctcaca tatacttaga ttacacaaag ataaagcttt agatgtgatc 180
attgtttaat gtgagcttat ctttaaaagt ttttaattaaa aactacagaa gggagtaaac 240
agcaagccaa atgatttaac caaatgattt aagagtaaaa ctactcaga aagcattata 300
cgtaactaaa tatacatgag catgattata tacatacatg aaactgcaat tttatggcat 360
tctaagtaac tcattttaagt acatttttgg catttaaaca aagatcaaat caagct 416

```

```

<210> 125
<211> 199
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(199)
<223> n = A,T,C or G

```

```

<400> 125
agcgtggctg cggccgaggt gctttttttt tttttttttt tttttttttt gctattctaa 60
aggggaaggc ccctttttat taaacttgta cattttactt tccttctttc anaatgctaa 120
taaaaaactt ttgtttatac ttaaaaaaac cataaatcan acaaacaaaa gaaacgattc 180
caacatcact tctgngatg 199

```

```

<210> 126
<211> 490
<212> DNA
<213> Homo sapien

```

```

<400> 126
cgtggtcgcg gccgaggtcc agttgctcta agtggtattg atatggttgg agtggcacag 60
actggatctg ggaaaacatt gtcttatttg cttcctgcca ttgtccacat caatcatcag 120
ccattcctag agagagggcga tgggcctatt tggttggtgc tggcaccaac tcgggaactg 180
gcccaacagg tgcagcaagt agctgctgaa tattgtagag catgtcgctt gaagtctact 240
tgtatctacg gtggtgctcc taagggacca caaatcgtg atttgagag aggtgtggaa 300
atctgtattg caacacctgg aagactgatt gacttttttag agtgtggaaa aaccaatctg 360
agaagaacaa cctaccttgt ccttgatgaa gcagatagaa tgcttgatat gggctttgaa 420
ccccaataaa ggaagattgt ggatcaaata agacctgata ggcaaaactct aatgtggagt 480
gcgacttggc 490

```

```

<210> 127
<211> 490
<212> DNA
<213> Homo sapien

```

```

<400> 127
cgtggtcgcg gccgaggtcg gccgaggtct ggagatctga gaacgggcag actgcctcct 60
caagtgggtc cctgaccctt gaccccccag cagcctaact gggaggcacc ccccagcagg 120
ggcacactga cacctcacac ggcagggtat tccaacagac ctgaagctga ggtgcctgtc 180
tgttagaagg aaaactaaca agcagaaagg acagccacat caaaaaccca tctgtacatc 240
accatcatca aagaccaaaa gtaataaaaa ccacaaagat gggaaaaaaa cagaacagaa 300

```

```

aaactggaaa ctctaaaaag cagagcacct ctcctcttcc aaaggaacgc agttcctcac 360
cagcaatgga acaaagctgg atggagaatg actttgacga gctgagaaaa gaacgcttca 420
gacgatcaaa ttactctgag ctacgggagg acattcaaac caaaggcaaa gaagttgaaa 480
actttgaaaa

```

```

<210> 128
<211> 469
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(469)
<223> n = A,T,C or G

```

```

<400> 128
cgtggctcgc gccgaggtgc tttttttttt tttttttttt tttttttttt tgctgattta 60
ttttttctnt ttattgttac atacaatgta taaacacata aaacanaaaa cagtagggat 120
cctctaggat ctctagggan acagtaaagt anaaagaggt ctcanaaaca ttttttttaa 180
gtacaagaca ttcagnctc ggcccaaagg cgtaaaaggt ttanagccag canatagctg 240
nactaaaggc tccgtctntn tccccanagc caggacaacc ccaggagct ntccattagc 300
agccagtgca cgcaggcagg atgctgcgga aaaagctcta tgctganaac attccccttg 360
atggaaagaa gggcaacaca aaaggggtaa ctaanagctc cttcctctcg tgagggcgac 420
aactgaggaa cagaaaagga gtgtcccatg tcacttttga cccctctcc 469

```

```

<210> 129
<211> 419
<212> DNA
<213> Homo sapien

```

```

<400> 129
gcgtggctgc ggccgaggtc tgattttcat ttaaataattt cagagctata gcatttgcct 60
ccatgctcaa atccacacca ttggggctta agccgctcat gccaacatta gcaaatgaca 120
tgcagtttaa tccagagatc actgcttctg ggctgatgca tgccaacaca ctggcgtgat 180
ccacgttatg tgcatttttc ttcacttttag tgggagaatc aatttttact ccaaggcttc 240
ttagttgctt aagagttgca ttaaggacac aatctttgtc caccagtctt gaatgatgtg 300
tttttttctt tgtatggtaa acgttttggt ttctgggtga ttcatgactg ataattactg 360
ctttggtaga cggctgctca agtttccttg gaggaactat ttaataggtg ggttacttg 419

```

```

<210> 130
<211> 354
<212> DNA
<213> Homo sapien

```

```

<400> 130
agcgtggctc cgcccgaggt ccatctgagg agataaccac atcactaaca aagtgggagt 60
gaccccgtag agcacgctgt ggaattccat agttggtctc atccctggtc agtttccaca 120
tgatgatggt cttatctcga gagggcgaga ggatcatgtc cgggaactgc ggggtagtag 180
cgatctgggt taccagccg ttgtggccct tgaggggtgc acgaagggtc atctgctcag 240
tcatggcggc ggcgagagcg tgtgtcgtg cagcgacgag gatggcactg gatggcttag 300
agaaactagc accacaacct ctctgcccgc acctgcccgc gcggcccgtc cgaa 354

```

```

<210> 131
<211> 474
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(474)
<223> n = A,T,C or G

```

```

<400> 131
cgagcgccg cccgggcagg tctggcagca gcttctctg gaataattga cagctttgtg      60
ctgcctgact aaaatttgaa atgacaaccg ctgaatgtaa aatgatgtac ctacaatgag      120
agagatttag gaatactatc tgtcaatcca tagatgtaga aacaaaacaa actacagaat      180
gaaaacaaac ttattttaaa ccaaagaaac aaatgtatcc aaaatatagt ccatgatata      240
tttgattact agtataacca cagttgaaaa cttaaaaaaa aaaattgaca ttttttgtaa      300
tgggtactaa tggatttata aaaggtttct gtttccaaag atgttattgg ggtccacata      360
ttccttgaag accttcagcat cccaaagccc gacatcagag atactttcct ttagccattg      420
nttcccgtaa cttgcccact ccatggtgat gtgacaggct tcccttcatt agca          474

```

<210> 132

<211> 474

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(474)

<223> n = A,T,C or G

```

<400> 132
ggccgaggtg gggaattcat gtggaggtca gagtggaagc aggtgtgaga gggtcacgca      60
gaaggaaaca tggctgccaa agtgtttgag tccattggca agtttggcct ggccttagct      120
gttgaggag gctgtggtgaa ctctgcctta tataatgtgg atgctgggca cagagctgtc      180
atctttgacc gattccgtgg agtgcaggac attgtggtag ggggaaggac tcattttctc      240
atcccgtggg tacagaaacc aattatcttt gactgccgtt ctcgaccacg taatgtgcca      300
gtcatcactg gtagcaaaga tttacagaat gtcaacatca cactgcgcac cctcttccgg      360
cctgtcgcca gccagcttcc tcgcattctc accagcatcg ganaggacta tgatgaaccg      420
tgtgtcgccg tccatcacaa ctgagatcct caagtcagtg gtggctcgct ttga          474

```

<210> 133

<211> 387

<212> DNA

<213> Homo sapien

```

<400> 133
tgctcgagcg gccgccagtg tgatggatat ctgcagaatt cggccttagcg tggtcgcggc      60
cgaggtctgc gggcccctta gcctgccctg cttccaagcg acggccatcc cagtagggga      120
ctttcccaca ctgtgccttt acgatcagcg tgacagagta gaagctggag tgcctcacca      180
cacggcccgg aaacagcggg aagtaactgg aaagagcttt aggacagctt agatgccgag      240
tgggcgaatg ccagaccaat gatacccaga gctacctgcc gccaaacttg tgagatgtgt      300
gtttgactgt gagagagtgt gtgtttgtgt gtgtgttttg ccatgaactg tggccccagt      360
gtatagtgtt tcagtggggg agaactg

```

<210> 134

<211> 401

<212> DNA

<213> Homo sapien

```

<400> 134
ggccgcccgg gcaggtctga tgaagaacac ggtgtgtatc cttgccaatg acgccaatgc      60
tgagcggtc aagagtgttg tgggcaactt gcatcggtcg ggagtcacca acaccattat      120
cagccactat gatgggcgcc agttcccaa ggtggtggg ggctttgacc gactactgct      180
ggatgctccc tgcagtggca ctgggtcat ctccaaggat ccagccgtga agactaacia      240
ggatgagaag gacatcctgc gcttgtgctc acctccagaa ggaagtgtct cctgagtgtc      300
attgactctt gtcaatgcga ccttcaagac aggaggctac ctggtttact gcacctgttc      360
tatcacagtg agacctctgc catggcagaa caggggaagc t

```

<210> 135

<211> 451

<212> DNA

<213> Homo sapien

35

```

<400> 135
ggtcgcggcc gaggtctgtt cctgagaaca gcctgcattg gaatctacag agaggacaac      60
taatgtgagt gaggaagtga ctgtatgtgg actgtggaga aagtaagtca cgtggggccct      120
tgaggacctg gactgggtta ggaacagttg tactttcaga ggtgaggtgt cgagaaggga      180
aagtgaatgt ggtctggagt gtgtccttgg ccttggctcc acaggggtgt ctttcctctg      240
gggccgtcag ggagctcatc ccttgtgttc tgccagggtg ggtaccggg gtttgacact      300
gaggagggtg acctgctggc tggagcggca gaacagtggc cttgatttgt cttttggaag      360
attttaaaaa ccaaaaagca taaacattct ggtccttcac aatgctttct ctgaagaaat      420
acttaacgga aggacttctc cattcaccat t                                451

```

```

<210> 136
<211> 411
<212> DNA
<213> Homo sapien

```

```

<400> 136
ggccgcccgg gcaggctctga atcacgtaga atttgaagat caagatgatg aagccagagt      60
tcagtatgag ggttttcgac ctgggatgta tgtccgcgtt gagattgaaa atgttccctg      120
tgaatttgtg cagaactttg acccccttta ccccatattc ctgggtggct tgggcaacag      180
tgagggaagt gttggacatg tgcagggtgg tccctttgct gcgtatttgg tgcctgaggc      240
tctgtggatt tcccctccat caatcatctt accctctcat cccctcaga tgcgtctgaa      300
gaaacatctc tgggtataaga aaatcctcaa gtccaagat ccaatcatat tttctgtagg      360
gtggagggaag tttcagacca tcctgctcta ttatatccga agaccacaat g                                411

```

```

<210> 137
<211> 211
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(211)
<223> n = A,T,C or G

```

```

<400> 137
cgccgcgccg ggcaggctcg ttggtgcggc ctccattgtt cgtgttttaa ggcgccatga      60
ggggtgacag aggcggtggt cgtggtgggc gctttggttc cagaggaggc ccaggaggag      120
ggttcaggcc ctttgaccca catatcccat ttgacttcta tttgtgtgaa atggcctttc      180
cccgnntcaa gccagcacct cgatgaaact t                                211

```

```

<210> 138
<211> 471
<212> DNA
<213> Homo sapien

```

```

<400> 138
gccgcccggg caggctctgg ctggcgactg gcatccaggc cgtaactgca aatctatgct      60
aggcggggtc tcccttctgt gtgttcaagt gttctcgact tggattctta actattttaa      120
aaaatgcact gagtttgggt taaaaaccaa ccacaaaaat ggatttcaac acagctctaa      180
agccaagggc gtggcgggct ctcccaacac agcgactcct ggaggccagg tgcccatggg      240
cctacatccc ctctcagcac tgaacagtga gttgattttt ctttttacaa taaaaaaagc      300
tgagtaatat tgcataggag taccaagaaa ctgcctcatt ggaacaaaaa actatttaca      360
ttaaataaaa agcctggccg caggctgcgt ctgccacatt tacagcacgg tgcgatgcac      420
acggtgacca aaccacggag gcaagcttct ggcactcaca ccacgaccg c                                471

```

```

<210> 139
<211> 481
<212> DNA
<213> Homo sapien

```

```

<220>

```

36

<221> misc_feature
 <222> (1)...(481)
 <223> n = A,T,C or G

<400> 139
 gtcgcgccg aggtctgttc tttagctcag atttaaacct gctgtctctt ctttatttgc 60
 agaatgaatt cccagttcct gagcagttca agaccctatg gaacgggcag aagttgggtca 120
 ccacagtgc agaaattgct ggataagcga agtgccactg gggtctttgc cctcccttca 180
 caccatggga taaatctgta tcaagacggt tcttttctag atttcctcta cctttttgct 240
 cttaaaactg cttctctgct ctgagaagca cagctacctg ccttcaactga aatatacctc 300
 aggctgaaat ttgggggtggg atagcaggtc agttgatctt ctgcaggaag gtgcagcttt 360
 tccatatcag ctcaaccacg ccgncagtc attcttaagg aactgccgac taggactgat 420
 gatgcatttt agcttttgag cttttggggg gtattctacc aaccaacagt ccatttgga 480
 a 481

<210> 140
 <211> 421
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(421)
 <223> n = A,T,C or G

<400> 140
 gtcgcgccg aggtttccca ttttaagaaa atagatcttg agattctgat tcttttccaa 60
 acagtcocct gctttcatgt acagcttttt ctttacctta cccaaaattc tggccttgaa 120
 gcagttttcc tctatggctt tgcctttctg attttctcag aggctcgagt ctttaataata 180
 accccaaatg aaagaaccaa ggggaggggt gggatggcac ttttttttgt tggctttgtt 240
 ttgttttgtt ttttggttgg ttgggttccg ttatttttta agattagcca ttctctgctg 300
 ctatttcocct acataatgtc aatttttaac cataattttg acatgattga gatgtacttg 360
 aggccttttt gntttaattg agaaaagact ttgcaatttt ttttttagga tgagcctctc 420
 c 421

<210> 141
 <211> 242
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(242)
 <223> n = A,T,C or G

<400> 141
 cgantngccc gcccgggcan gtctgtctaa nttntcang gaccacgaac agaaactcgt 60
 gcttcaccga anaacaatat cttaaacatc gaanaattta aatattatga aaaaaaacat 120
 tgcaaaatat aaaataaata nnaaaaggaa aggaaacttt gaaccttatg taccgagcaa 180
 atccaggtct agcaaacagt gctagtcccta nattacttga tntacaacaa cacatgaata 240
 ca 242

<210> 142
 <211> 551
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(551)
 <223> n = A,T,C or G

```

<400> 142
agcgtgggtcg cggcncgang tccacagggc anatattctt ttagtgtctg gaattaaaat    60
gtttgagggtt tangtttgcc attgtctttc caaaaggcca aataattcan atgtaaccac    120
accaagtgc aacctgtgct ttctatttca cgtactgttg tccatacagt tctaaataca    180
tgtgcagggg attgtagcta atgcattaca cagtcgttca gtcttctctg cagacacact    240
aagtgatcat accaacgtgt tatacactca actagaanat aataagcttt aatctgaggg    300
caagtacagt cctgacaaaa gggcaagtgt gcataataga tcttcgatca attctctctc    360
caaggggccc gcaactaggc tattattcat aaaacacaac tgaanagggg attggtttta    420
ctggtaaadc atgtgntgct aaatcatttt ctgaacagtg gggctctaat cantcattga    480
tttagtgcca gccacctgcc cggcgcccg ntcgaagccca attctgcaga tatccatcac    540
actggcgcc g                                     551

```

```

<210> 143
<211> 515
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(515)
<223> n = A,T,C or G

```

```

<400> 143
cgagngggccc gcccgggcag gtatcttcac aaactcaaca aaggcactac atgagacttc    60
acattcccct agtccaatag ctgacaaatt tttgcaacgt tctgcaatgc gaattaactc    120
ttcatcaagt ggccgtaatc catttgacac cactactagt tcaaccagtc tagggcatgt    180
cattcccaca cggccaagca catctttgct tactgatctc ccaaagtaca gatgggtggc    240
aggtatttca tagcgaaaga aggggtcaaa ttcttcttca tataanaaaa aatacatcac    300
taagttcact ttgggtgaat gtctgatgaa agcatcccag ctactcttct gaatagtatg    360
gaagtgtgtc tgtccaggat tctcactgac tacatcaatg cgcaaagtgt ctaatcgaac    420
atgtttttca gaagacaatg caagtaacaa ctcatcactc aataagtggg aagttcaggg    480
ctagttctct taagccgnga cactgatcag cacac                                     515

```

```

<210> 144
<211> 247
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(247)
<223> n = A,T,C or G

```

```

<400> 144
tgcattctct ntggatgcan acctgcccgt tggtagggac tntgctcaca cggaacatgg    60
acggttacac ctgtgccgtg ggtgacgtcc accagcttct ggatcatctc ggcgnggggtg    120
ttgtggaagg gcagactatc cacctccatg cncacgatgc ccganacgcc actccggact    180
ntgtgctgca ccaanatgcc cagcattnta tcttcaagca naggcattat cagggtcctt    240
gacacac                                     247

```

```

<210> 145
<211> 309
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(309)
<223> n = A,T,C or G

```

```

<400> 145
cgtgggtcgc ggcccgangt ctgctgtaac aaaacacccat agtctgggca gctcatagac    60

```

38

```

aatggaattt tatttctcac gcttctggag gctggattcc aagatcaagg ttccaggaga 120
ctcagtgctt ggcaaggctt cggtttctgc ctcanagatg gtgccatctg gctgtgtcct 180
cacaagtagg aagggtgcaag aagctcccct caggctctgt ctgtaagaca ctgatcccat 240
tcatganggg gaaacgtaat gacctaatca gccccagag accccacttc taacaccatc 300
accttgggg 309

```

```

<210> 146
<211> 486
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(486)
<223> n = A,T,C or G

```

```

<400> 146
agcgtgggtc gcggcncgac gtctgtcca tatttcacag cccgagaact aatacaagat 60
gctgacatca tattttgtcc ctacaactat cttctanatg cacaaataag ggaaagtatg 120
gatttaaatc tgaagaaca ggttgctcatt ttanatgaag ctcataacat cgaggactgt 180
gctcgggaat cagcaagtta cagtgtaca gaagttcagc ttcggtttgc tcgggatgaa 240
ctanatagta tggtaacaa taatataagg aaganagatc atgaaccctt acgagctgtg 300
tgctgtagcc tcatataatt gntagaagca aacgctgaat atcttgnana angagantat 360
gaatcagctt gtaaaatatg gagtggaaat gaaatgctt taactttaca caaaatgggt 420
atcaccactg ctacttttcc cattttgcng gtaagatatn ttttctacct gngaaacgta 480
ttaag 486

```

```

<210> 147
<211> 430
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(430)
<223> n = A,T,C or G

```

```

<400> 147
gccgcccggg cangttcgac attacntnga gttccatgat gtacaattct ttcacgaaaa 60
acaatgaatg caagaatttg aggatctcct tactcctccc ttttacagat ggtctctcaa 120
tcccttcttc ttctcttcca tttcatctt cttctgaacg cgtgcggg taccacggct 180
ttctttgtct ttatcgtgag atgaaggatg tgcttctgtt ttttctacca taactgaaga 240
aatttcgctg caagtctctt gactggctgt ttctcogact tcgccttnt gtcaaacgng 300
agtcttttta cctcatgccc ctacagttca cagcatcttc atctggatgt tnattttctca 360
aagggtcac tgaggaaact tctgattcan atgtcgaana gcactgtgaa gttttctctt 420
cattttgctg 430

```

```

<210> 148
<211> 483
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(483)
<223> n = A,T,C or G

```

```

<400> 148
cccgggcagg tctgtgttgn tttncacagg gtgtcctccc cagcgtccag aananggaaa 60
tgtggagcgg gtgatgatga cccctcgctg tcctgtcacc tcctgcacag cttcgtatgt 120
gggtctggtc tgggaccacc cgtacagggt gtgcacgttg tagtgctcca cgggggagct 180
gtccggcagg atctgctgac tctccatgca cagagtcctg ctgctcaggc ccttgtccct 240

```

```

agattccaaa tatggcatat aggggtgggt tatttagcat ttcattgctg cagcccctga 300
cagatccatc cacaaaattt gatggctcat tcatatcaat ccacaatcca tcaaacttca 360
agctctttctc tggntctoga nggtttgcat agaactcttc tatctctttc ttccaccacg 420
canacctcgg ncgcgaccac gctaagccga attctgcana tatccatcac actggcggcc 480
gct 483

```

```

<210> 149
<211> 439
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(439)
<223> n = A,T,C or G

```

```

<400> 149
ctttcacgaa nacaatgaat gcaagaattt gaggatctcc ttactcctcc cttttacaga 60
tggctctctca atcccttctt ctctctcttc atcttcatct tcttctgaac gcgctgccgg 120
gtaccacggc tttctttgtc tttatcgtga gatgaagggt atgcttctgt ttcttctacc 180
ataactgaag aaatttcgct gcaagtctct tgactggctg tttctccgac ttgcctttt 240
tgcaaacgtg agtcttttta cctcatgccc ctacagcttc acagcatctt catctggatg 300
ttcatttctc aaagggtcga ctgaggaaac ttctgactca catgtcgaag aagcactgng 360
agtttctctt catttgctgc aaanttgtc tttgctggct gngctctcag accaccatt 420
tggtgcatg ggggctgac 439

```

```

<210> 150
<211> 578
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(578)
<223> n = A,T,C or G

```

```

<400> 150
ggcncgccc ggcangtcca ctccactttt gagctctgag ggaatacctt caggagggac 60
agggtcagg agtcctggca gctcgcgagc agagattcac attcattcag agacttggtg 120
tccagtgcaa tgccattgat cgcaacgac ctgtctccca cagcaaggga cccttcttta 180
gcggcaggc ttcaggcag cacagcggca gcatacactc cattctccag actgatgcca 240
ctgtctttct gtccactgan gttgatgtgc agcggcgtga ccaccttccc acccagggac 300
ttcctccgcc gcacgaccat gttgatgggc cccctncca ttgaggagcg ccttgatggc 360
ctgcttcttg nccttggtga tgaagtccac atcggtgatt ctacagcca gtcattgacc 420
cttaagcgg catcagcaat gcttcctttg gccactttag ngacaaatat gccacagtcc 480
ccgggaaaca agggtcattc acaccttctg gcatatcaaa cacctcggcc ggganacta 540
agccgaattc tgcagatatc catcacactg gngggccg 578

```

```

<210> 151
<211> 503
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(503)
<223> n = A,T,C or G

```

```

<400> 151
cgagcggccc gcccgggcag gtctgggaga tcagcgactg ctgccacgtg cccagaaatg 60
gctcgtctct tcaactacagc ggaatgcaat gaggggtggg gagaagatga tgggtcggtt 120
atttcattcc ttttcttttt acaacttcac tttcagagac ttcagcggtc catgtctgct 180

```



```

gtgctgtgga acccagagt ctcttgccctg gatggctgag aatcccttgg accctggaag 240
cacctactcc atgatggccc ggtatagtgc aggtcacaata taatcttccc ggtatcttga 300
gttgataact cgttgccggt tcttttcttg cttaacctct ttctctgtga aaatctcatt 360
gaagcgcatg tctgaagcta ctgacagtct anatttgact ctcttgggaa gctcttcac 420
cagtgtgtat acatcatctc tcttaaccac aagttggagc catncttaaa cttcacctgg 480
tacatttgga taggggtgga ggc

```

<210> 152

<211> 553

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(553)

<223> n = A,T,C or G

<400> 152

```

agcgtggtcg cggcccgagg tccactgagc tccgccttcc cggggctccc tgaggaagca 60
gagtcctgac ttccaggaag gacaggacac agaggcaaga actcagcctg tgaggctctg 120
ggtggctcct gaggccagag gacgccttcc gcgatccatg gctcagcatc gtccttctgg 180
cttcccagcc cggggccgaa cgttcggggt aataagcaga gcagttattc ggctcctggc 240
aggagctccc ccgttagttt ccacgttggt agcacattca tacttaagac tgnntctctt 300
tgtgttttaa gcgtctgtct ctgtagttaa ctgaaatgtt aacagaaatg cagacctgcc 360
cgggcggcgg ctcgaaagcc gaattctgca gatattccat acactggcgg ccgctcgagc 420
atgcatctag anggccaat tcgccctata gtgagtcgna ttacaattca ctgggcccgcg 480
ntttacaacg tcgtgactgg gaaaaccctg cggtagccac ttaatcgctt tgcagnacat 540
ccccctttcg cca

```

<210> 153

<211> 454

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(454)

<223> n = A,T,C or G

<400> 153

```

tcgagcggct cgcccgagg ggtccaccta gcatggctcc tctaaacacg caactcagcg 60
aggggacccc cttcacctct ggcaagagag ctgggtagat cagaaaactg gtgacacctg 120
gctagcacag agcaggetca cttgtcttgg tccactacc cagattcctg cagacattgc 180
aaaccaaag aaggttgntg aatgaccctt gtccccagcc acttgttttg gtatcatctg 240
ctctgcagtg gaatgcctgt gtgtttgagt tcaactctga tctgtatatt tgagtataga 300
aaccgantca agtgatctgt gcatncagac acactggggc acctgancac agaacaaatc 360
accttaacga tctggaatga aactgnganc antgcccgcc tgggtgggtc tgganaaact 420
gccgncttct tggtggacct tggccgcacc acct

```

<210> 154

<211> 596

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(596)

<223> n = A,T,C or G

<400> 154

```

agcgtggtcg cggcccgagg gcggcctcct gantganggg aagggaactg ggggcccga 60
cggcaggatt aacctccatt tcagctaatac atgggagaga ttaaagtctc tcttgattat 120

```

41

```

aactggttta naggtacagt tccccttaaa aagattattg tggatgatga tgacagtaag 180
atatggctgc tctatgacgc gggcccccga agtatcaggt gtccctctcat attcctgccc 240
cctgtcagtg gaactgcaga tgtctttttc cggcagattt tggctctgac tggatggggg 300
taccgggtta tcgcttttga gtatccagtt tattgggacc atctcgagtt cttgtgatgg 360
attcacaaaa cttttanacc atttacaatt ggataaagtt catctttttg gcgcttcttt 420
gggangcttt ttggcccan aatttgctga atacactcac aaatctccta gaagccattc 480
cctaatactc tgcaattcct tcagngacac ctctatcttc aaccaacttg gactggaaac 540
agctttggct gatgcctgca tttatgctca aaaaatagtt cttggaaatt ttcac 596

```

```

<210> 155
<211> 343
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(343)
<223> n = A,T,C or G

```

```

<400> 155
ctcganttgg cncgcccggg cangtctgcc tggtttttga ccngcgcgagc tatttagnct 60
ctggctctgt ttccggagct caaggnaaaa atcttgaana actcgagcag cttctgtgga 120
tagccttggg tacacatact gccgagcata gccaatgtac tttctcaata gctgggtggg 180
aatgggatct attgtttctc caggaaccac ctttagtctt tctgataatg gcttctcaga 240
aactacttca agtacggaag tatttgaatc ttgactatnc atacgagcta ctgtggcact 300
gctaattggn tctctgctnt ccagctctta ttgcaatcac atg 343

```

```

<210> 156
<211> 556
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(556)
<223> n = A,T,C or G

```

```

<400> 156
tcgagcggcc cgcccgggca ggtctggcac cacncagatc gattaactgg ctcatctgat 60
ctcgtggccc ccaccctgga actgacttag cacaaaagga cacctcaatt cttatgatt 120
tcattctcga cccaaccaat caacaccctt gactcactgg ccttcccctt cccaccaa 180
tatccttaaa aactctgatc cccgaatgct caggagatc gatttgagta ctaataagac 240
tccagtctcc tgcacaagca gctctgtgta ctcttctctt attgcaattc ctgtcttgat 300
aaatcggtc tgtgtaggcg gcggaagaag tgaacctgtt gggcggttac cacctctgtc 360
gtgtgtgaca gttgntttga atctctaatt gctcagtaca gatccacatg caggtttaagt 420
aagaagcttt tgaagaaaat ggaaagtctt aagtgatggc ttccaagaaa tcaaacctac 480
attaattagg gaacaacgga ctttacgtat cacaaatgaa gagactgacn aagtaaatca 540
acttggcctt ttctta 556

```

```

<210> 157
<211> 333
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(333)
<223> n = A,T,C or G

```

```

<400> 157
ggtcacaaa aatatatnaa ataagctgga tatataaaan caaacactta acatngnca 60
cattccttca gttattcaaa ctactgata nctaacngg agnagttggn attctggaa 120

```

42

```

acttcctaag ctaaaagtat atttacatat ttacaacaca ngtaaatata acngaagaac 180
tacttcaaat aangnnngaaa ttccagaatt ctanagattt atagctatag ntnacaanta 240
tcaccaattg gtttgcaatc aanngnccag cactacttat gannaangtt taactannaa 300
accaaaaagg gagaaaacct ggnagggaaa nat 333

```

```

<210> 158
<211> 629
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(629)
<223> n = A,T,C or G

```

```

<400> 158
tcgagcggcc gcccgggcag gtctggtaca tttgtgagag gtccggcact ctgtttctcat 60
ccagtaagtg gtcgagccct ttctgcagaa ttgctgttaa atgtttctct aatagctgtt 120
tctccacaca agcaatcagt ggtttctgtg tgctgtggtc caagtaagtg attactctgt 180
ctccctcttc ttctaagcgt ttacttacat ggtaaagata ttctggaacc tctctttcct 240
gcattaacct ttggccttcg gcagcatata agcaattagt ctcttccaaa aatttcagtt 300
caaatgaatc ttatacacc tgcaggtcag acagcatgcc caggagggtc ccgcaacagg 360
ctccggtcca cggcctcgcc gctcctctcg cgctcgatca gcagtaggat tccatcaatg 420
gttttactct gaaccatttt atcactaata atatgggttc taaacagttc taatcccata 480
tcccagatgg agggcagcgt ggagttctgc agcacatagg tgcggtccaa gaacaggaag 540
atgcttctga tcatgaatca tttgntctgg aatggctctg ccagcacgtg gtaatctttc 600
ttttaaaaat aaacccttat ctaaacgtc 629

```

```

<210> 159
<211> 629
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(629)
<223> n = A,T,C or G

```

```

<400> 159
tcgagcggcc gcccgggcag gttctagagg ganaatctgg ctgatttggg aataaaatat 60
aatcgaaat tcaacacat gaagataaat cttattttgg aaatctactg accttaatac 120
cccaagcttg ccctgaatac ttgatttga attggaatat atcaaaaaag gttagtattt 180
ttgtgttagt taggatacta aaaggatatt agttacccaa gagatccaat ttgtttttct 240
gatgaatagt gttcagtaaa atgaagcagt cttagagtg actaataatt tcaaagtgat 300
ttttcgtcta ttcttaatat tttttaatta tttattttta agagttttat accttgagca 360
gatacaatga tccgcttttag tgagaggaca atttctgatt gattgttttc tcttcaggcc 420
atctcacctc ttcattctct tgttacattt gaagcagttg atataatggg tttatacttt 480
aaaagataga catggtgcca tgaagtttgg ggaagttggg tgaattatcc cattctagtt 540
acagangagc tttccttaaa tgccctttac ttctangttt ggtcaagaag tcattttctg 600
agtaaaagtt attttcatat atgttgggg 629

```

```

<210> 160
<211> 519
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(519)
<223> n = A,T,C or G

```

```

<400> 160

```

tcgagcggcg	cgcccgggca	ggtctgctgg	gattaatgcc	aagtntttca	gccataaggt	60
agcgaaatct	agcagaatcc	agattacatc	cacttccaat	cacgcggtgt	ttgggtaatc	120
cacttagttt	ccagataaca	tacgtaagaa	tgtccactgg	gttggaacc	acaattatga	180
tgcaatcagg	actgtacttg	acgatctgag	gaataatgaa	tttgaagaca	ttaacatttc	240
tctgcaccag	attgagccga	ctctcccctt	cttgctgacg	gactcctgca	gttaccacta	300
caatcttana	attgggcggg	tcacagaata	atctttatct	gccacaattt	taggtgctga	360
agaaataagc	tcccatgctg	cagatccatc	atttctnctt	taagcttata	ttccaaaaca	420
tccaacaagan	caangttcat	cagccagaga	ctttcccaga	atgctgatag	nacacgccat	480
accaacttgt	ccaacancca	ctacagcgat	cttatttgtt			519

<210> 161

<211> 446

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(446)

<223> n = A,T,C or G

<400> 161

cgagngggcc	gccccggcag	gtccagtaag	cntttnacga	tgatgggaaa	ggttatgcaa	60
ggtcccagcg	gtacaacgag	ctgtttctac	atcatttgta	ttctgcatgg	tacgtacaat	120
agcagacacc	atctgaggag	aacgcataat	agcgtgtctg	gaagcttcct	ttttagaaag	180
ctgatggacc	ataactgcag	ccttattaac	caccacctgg	tcctcgtcat	ttagcagttt	240
tgtcagtcca	gggattgcac	gtgtggcang	ttctgcatca	tcttgatagt	taatcaagtt	300
tacaactggc	atgtttcagc	atctgcgatg	ggctcagcaa	acgctggaca	ttantgggat	360
gagcagcatc	aaactgtgta	natgggatct	gcataccctc	atctaattgc	tcagggaaca	420
tagcagctcg	tacctctga	gctcga				446

<210> 162

<211> 354

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(354)

<223> n = A,T,C or G

<400> 162

agcgtngtcg	cggcccggag	tcctgggaag	cctttnttgc	tgagcctcac	agcctctgtc	60
aggcggctgc	ggatccagcg	gtccaccagg	ctctcatggc	ctccgggctg	ggaggngggg	120
gagggcacaa	aacccttccc	aaggccacga	anggcaaact	tggtggcatt	ccanagcttg	180
ttgcanaagt	ggcggnaacc	cagtatccgg	ttcacatcca	ggntgatgtc	acgaccctgg	240
gacatgtang	cacataatcc	aaaccggaga	gcatacgggc	cacattcacg	aatccccgct	300
gggaagtcag	ctttctgccc	ttctttggcc	ttctccacct	cgtggggtac	cagg	354

<210> 163

<211> 258

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(258)

<223> n = A,T,C or G

<400> 163

tttttcncca	agtcctcttg	ccnggggatc	tngactgcaa	tttaagacac	ttctaattag	60
ttataccag	gccctgcaaa	attgctgggt	ttatataata	tattcttgct	gcacgaagat	120
ttattattct	gttggtgatg	tctattttaa	ttntatttat	tctggccaaa	aaagaacctt	180

ctccgctcgt caagagangc caatntgtct tgaaggacaa gagaaagatg ctaacacaca 240
ctttcttctt cttgagga 258

<210> 164
<211> 282
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(282)
<223> n = A,T,C or G

<400> 164
ggaacatatt actttttaaact tacttgggtc aatgaaacat ttaataaaaa catttgcttc 60
tctatataat acgtatgtat aaaataagcc ttttcanaaa ctctgggttct cataatcctc 120
tataaatcan atgatctgac ttctaagagg aacaaattac agnaaggggt atacattnat 180
gaatactggt agtactagag ganngacgct aaaccactct actaccactt gcggaactct 240
cacagggtaa atgacaaaagc caatgactga ctctaaaaac aa 282

<210> 165
<211> 462
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(462)
<223> n = A,T,C or G

<400> 165
gcccgggcan gtcctgtaac cccagctact cangangctg agtcatgana atcgctgaa 60
tccgggaggt agaggccgca gcgagcaaag attaagccac tgcactocag tctgggtgac 120
agagtggagaa tctgtctgtt gtcctctgtg cattgggtctg aaatgggttt gtagaacatg 180
ccacagaagg accagcanca gcaacaaatg gatttgtgga angcgtagct ccaaattggag 240
cangcacact tgatgaagca cgctgtgtct gtgcagangc aaccactggc actgttccaa 300
aaacattgct gctagcatta cttgtggaag tatacgcatc actggagggt gctgcanaac 360
tgaaaacgct gtctagtctt gccanagctg catacttgnc tgaanatgca cttgactgac 420
tggggaactga accacanaac caacaggacc tttacctgtg ga 462

<210> 166
<211> 365
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(365)
<223> n = A,T,C or G

<400> 166
cgtgggtcgc ggcncgangt ctgaaaccaa tccagaacta aacatcagca cacaaaaaat 60
accaggatag atggaatcaa aagactctga agccaaaagg aggctaggga gagcaactga 120
acttagcaag ctgaggactt cagtgtccat catccgatcc tgccctgtaa caacaggtct 180
atatgataga gatattccat ctgagctgga ggccattatc cttagcaaac taacacagaa 240
cagaaaacca aatacatggt ctcatcttaga agtaggagct aaatgatgag aactcaagga 300
cacaaaagaaa ggaacaacag aactggggc ctacttgagg gtggagggtg ggaggaggga 360
gaaga 365

<210> 167
<211> 364
<212> DNA

45

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(364)

<223> n = A,T,C or G

<400> 167

agcgtggtcg	cggcgcgang	tccagcccta	gcttgccgtg	gactccgcct	tcactgggtg	60
ctctctctaa	aagttgctga	ctctttactg	tatctcccaa	ttcccactcc	attggttcca	120
taaggggagg	ggtgtctcac	tcaacatggt	gttcctggta	ccaagaactg	gctgacgaag	180
ctgggtgccg	tggtcatgc	ctgtaatccc	agcacttttg	ggaggccaag	aaggcgcat	240
cacctgaggt	ctggagtcca	agatcagcct	gaccaacatg	atgaaaccaa	gtctccacta	300
aaaatataaa	acaattagcc	aggcatggtg	gtgggtgcct	gnaatcccag	ctactgggga	360
ngct						364

<210> 168

<211> 447

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(447)

<223> n = A,T,C or G

<400> 168

cccgggcagg	tcaaaaccca	aaacctttca	ttttagccca	aaccagctca	tgattaggta	60
tacaaggata	acagaaccag	ttgtcaggac	gagcatttga	caagtaaaag	caattcttgc	120
aaagctgcag	ttcatccagc	tcatggcatg	tgtctttata	tagcatcctc	gcaatgtcag	180
cttgctcact	gtctgtctcca	tagaaaaatca	cggatatttg	gagaagcaat	tgggcatcag	240
ctttgaactc	ttcataactt	cggatatttc	cttcattcac	tttctcttga	atggtgggaa	300
cgtccacaga	cctcggccgc	gaccacgcta	agcccgaaat	ctgcagatat	ccatcacact	360
ggcggccggt	cgagcatggc	atctagaagg	cccaattcgc	ctatagnag	tcgnattacc	420
aattcactgg	ccgtcgnntt	acaacgc				447

<210> 169

<211> 524

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(524)

<223> n = A,T,C or G

<400> 169

cgantngcgc	gcccgggcag	gtctgagcag	cctttctggn	tgctggacta	ttgggattgg	60
gttcatccaa	cagagactgt	atggatgtta	gaatggaaga	cacatcatag	gttggactcc	120
aacggttctg	aagtatgtcc	agacatatac	taccatctgc	atagactaag	aacaaagaag	180
taggtacatt	aaacgtaaca	agaccactaa	ggttttaaca	ttatagacaa	aacanaaata	240
gtcaaganta	ctttgctttt	gaagttttaa	gattcctatg	ttgcttccca	gttaactgcc	300
taaaaagata	agncataacc	accactagtg	aaataatcan	gatgatcaga	gaatgtcana	360
tgtgatcagt	ataaaactgg	angatattna	gtgtcatcct	ttggaaaagg	ctgccctatn	420
atccaggaaa	tcanaaacat	tnttgaacag	ggnccttagc	tatccacaga	catgtgggaa	480
attcattccc	caaatngtag	gctggatccc	ctatctgaaa	taac		524

<210> 170

<211> 332

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(332)
 <223> n = A,T,C or G

<400> 170
 tcgancggcn cgcccgggca ggtgacaaac ctgttattga agatgttggt tctgatgagg 60
 aanaanatca gaagggatgg tgacaagaan aanaanaaga agattaagga aaagtacatc 120
 gatcaagaag agctcaacaa aacaaagccc atctggacca gaaatcccga cgatattact 180
 aatgangagt acggagaatt ctataanagc ttgaccaatg actgggaaga tcacttggca 240
 gtgaagcatt tttcagttga nggacagttg gaattcagag cccttctatn tgtcccacga 300
 cgtgctcctt ttgatctgtt tganancaga aa 332

<210> 171
 <211> 334
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(334)
 <223> n = A,T,C or G

<400> 171
 cgagngggcnc gcccgggcag gtctgttgat agcgacttaa cagaaaagtc tagacaaaca 60
 taagcataaa aaattacagt ctttctaccc ttgggaatgg ggagaaaaag gaatctctac 120
 cccaagacca gaaataataa gtccctgttc tggcctgaa catccagaat tatggaggct 180
 ttggcctgac accacattan aatttggtct ggaaatcaaa ctttaganac angagatcgt 240
 aagccatttt atactatcga cctaaattcc agtctaacgg ttcctttaca aagttgcgga 300
 aagccctctt atatgctagc tgtaggaaat atag 334

<210> 172
 <211> 439
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(439)
 <223> n = A,T,C or G

<400> 172
 agcgtggtcg cggcccgang tctgcctata aaactagact tctgacgctg ggctccagct 60
 tcattctcac aggtcatcat cctcatccgg gagagcagtt gtctgagcaa cctctaagtc 120
 gtgctcatat tgtgctgcca aagctgggtc catgacaact tctggtgggg cgagagcagg 180
 catggcaaca aattccaagt tagggtctcc aatgagcttc ctagcaagcc agaggaaggg 240
 cttttcaaag ttgtagttac ttttggcaga aatgtcgtag tactgaagat tcttctttcg 300
 gtggaagaca atggatttcg ccttcacttt ctgccttaat atccactttg gtgccacaca 360
 acacaatggg gatgnnttca cacacttngn accanatctc tatgccagnt aggccatttt 420
 ggaagnactt cganggtac 439

<210> 173
 <211> 599
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(599)
 <223> n = A,T,C or G

<400> 173

cgatnngccg	cccgggcagg	tcctgtaaaa	naggaaattc	agacatcgta	cgactcgtaa	60
ttgaatgtgg	agctgactgc	aatattttgt	caaagcacca	gaatagtgcc	ctgcactttg	120
cgaagcagtc	taacaatgtg	cttgtgtacg	acttgctgaa	gaaccattta	gagacacttt	180
caagagtagc	agaagagaca	ataaaggatt	actttgaagc	tcgccttgct	ctgctagaac	240
cagtttttcc	aatcgcatgt	catcgactct	gtgaggggcc	agatttttca	acagatttca	300
attaccaacc	cccacagaac	ataccagaag	gctctggcat	cctgctgttt	atcttccatg	360
caaacttttt	gggtaaagaa	gttattgctc	ggctctgtgg	accgtgtagt	gtacaagctg	420
tagttctgaa	tgataaattt	cagcttccctg	tttttctggg	tctcgctctg	ttgtccaggc	480
tggagtgcag	tggcgcggat	tacagctcac	tggagtcttg	acttcccagg	cacaagcaat	540
cctcccacct	cagcctccta	actacctggg	actaaaaatg	caccgccacc	acattccgg	599

<210> 174

<211> 458

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(458)

<223> n = A, T, C or G

<400> 174

tcgatttgcc	cgcccgggca	ggtccatgcn	gnttntgccc	attcccattg	ngcccagaca	60
ncccatcccc	gaggccgaca	tcgccatggt	catgttcatg	cccaccatgc	cctggctcat	120
ccctgcgctg	ttcccagag	gggccattcc	catggtgccc	gtcattacac	cgggcatggt	180
cataggcatg	ggtcccccca	ggagagggtt	agnttgaggc	cggacaggaa	gcatgtttga	240
tggagaactg	aggttcacag	nctccaaaac	tttgagtcat	cacattcata	ggctgctgca	300
tattctgtct	gctgaatcca	ttgtatncag	tgatggcctg	ctggggnttt	ggaaggctng	360
cataccaggt	agtaagntcg	tctaggctga	tgtttacacc	tggggtcaga	ccaagtanga	420
gggcaagggt	ttgctgactg	attttctgga	cccataatc			458

<210> 175

<211> 1206

<212> DNA

<213> Homo sapien

<400> 175

ggcacgagga	agttttgtgt	actgaaaaag	aaactgtcag	aagcaaaaaga	aataaaaatca	60
cagtttagaga	acaaaaaagt	taaatgggaa	caagagctct	gcagtgtgag	gtttctcaca	120
ctcatgaaaa	tgaaaattat	ctcttacatg	aaaattgcat	gttgaaaaag	gaaattgcca	180
tgctaaaaact	ggaaatagcc	acactgaaac	accaatacca	ggaaaaggaa	aataaatact	240
ttgaggacat	taagatttta	aaagaaaaga	atgctgaact	tcagatgacc	ctaaaactga	300
aagaggaatc	attaactaaa	agggcatctc	aatatagtgg	gcagcttaaa	gttctgatag	360
ctgagaacac	aatgctcact	tctaaattga	aggaaaaaca	agacaaaaga	atactagagg	420
cagaaaattga	atcacaccat	cctagactgg	cttctgctgt	acaagaccat	gatcaaattg	480
tgacatcaag	aaaaagtcaa	gaacctgctt	tccacattgc	aggagatgct	tgtttgcaaa	540
gaaaaatgaa	tgttgatgtg	agtagtacga	tatataacaa	tgagggtgctc	catcaaccac	600
tttctgaagc	tcaaaggaaa	tccaaaagcc	taaaaattaa	tctcaattat	gccggagatg	660
ctctaagaga	aaatacattg	gtttcagaac	atgcacaaag	agaccaacgt	gaaacacagt	720
gtcaaatgaa	ggaagctgaa	cacatgtatc	aaaacgaaca	agataatgtg	aacaaacaca	780
ctgaacagca	ggagtctcta	gatcagaaat	tatttcaact	acaaagcaaa	aatatgtggc	840
ttcaacagca	attagtctcat	gcacataaga	aagctgacaa	caaaagcaag	ataacaattg	900
atatttcattt	tcttgagagg	aaaatgcaac	atcatctcct	aaaagagaaa	aatgaggaga	960
tattttaatta	caataaccat	ttaaaaaacc	gtatatatca	atatgaaaaa	gagaaagcag	1020
aaacagaagt	tatataatag	tataacactg	ccaaggagcg	gattatctca	tcttcatcct	1080
gtaattccag	tgtttgcac	gtggttgttg	aataaatgaa	taaagaatga	gaaaaccaga	1140
agctctgata	cataatcata	atgataatta	tttcaatgca	caactacggg	tggtgctgct	1200
cgtgcc						1206

<210> 176

<211> 317

<212> PRT

48

<213> Homo sapien

<400> 176

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Met Gly Thr Arg Ala Leu Gln Cys Glu Val Ser His Thr His Glu Asn
 1          5          10          15
Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala
 20          25          30
Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys
 35          40          45
Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala
 50          55          60
Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg
 65          70          75          80
Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr
 85          90          95
Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu
100          105          110
Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp
115          120          125
His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His
130          135          140
Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser
145          150          155          160
Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala
165          170          175
Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp
180          185          190
Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln
195          200          205
Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn
210          215          220
Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp
225          230          235          240
Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln
245          250          255
Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile
260          265          270
Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu
275          280          285
Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile
290          295          300
Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Val Ile
305          310          315

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<210> 177

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Made in the Lab

<400> 177

ccaatcatct ccacaggagc

20

<210> 178

<211> 1665

<212> DNA

<213> Homo sapien

<400> 178

gcaaactttc aagcagagcc tcccgagaag ccattctgcct tcgagcctgc cattgaaatg

60

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caaaagtctg ttccaaataa agccttggaa ttgaagaatg aacaaacatt gagagcagat 120
cagatgttcc cttcagaatc aaaacaaaag aaggttgaag aaaattcttg ggattctgag 180
agtctccgtg agactgtttc acagaaggat gtgtgtgtac ccaaggctac acatcaaaaa 240
gaaatggata aaataagtgg aaaattagaa gattcaacta gcctatcaaa aatcttggat 300
acagttcatt cttgtgaaag agcaaggga cttcaaaaag atcactgtga acaacgtaca 360
ggaaaaatgg aacaaatgaa aaagaagttt tgtgtactga aaaagaaact gtcagaagca 420
aaagaaataa aatcacagtt agagaaccaa aaagttaaatt gggaacaaga gctctgcagt 480
gtgaggtttc tcacactcat gaaaatgaaa attatctctt acatgaaaat tgcattgtga 540
aaaaggaaat tgccatgcta aaactggaaa tagccacact gaaacaccaa taccaggaaa 600
aggaaaataa atacttttgg gacattaaga ttttaaaaga aaagaatgct gaacttcaga 660
tgaccctaaa actgaaagag gaatcattaa ctaaaagggc atctcaatat agtgggcagc 720
ttaaagttct gatagctgag aacacaatgc tcacttctaa attgaaggaa aaacaagaca 780
aagaaatact agaggcagaa attgaatcac accatcctag actggcttct gctgtacaag 840
accatgatca aattgtgaca tcaagaaaaa gtcaagaacc tgctttccac attgcaggag 900
atgcttgttt gcaaagaaaa atgaatgttg atgtgagtag tacgatatat aacaatgagg 960
tgctccatca accactttct gaagctcaaa ggaaatccaa aagcctaaaa attaatctca 1020
attatgccgg agatgctcta agagaaaata cattggtttc agaacatgca caaagagacc 1080
aacgtgaaac acagtgtcaa atgaaggaag ctgaacacat gtatcaaaac gaacaagata 1140
atgtgaacaa acacactgaa cagcaggagt ctctagatca gaaattattt caactacaaa 1200
gcaaaaaatat tgggcttcaa cagcaattag ttcatgcaca taagaaaagct gacaacaaaa 1260
gcaagataac aattgatatt cattttcttg agaggaaaat gcaacatcat ctctaaaaag 1320
agaaaaatga ggagatattt aattacaata accatttaaa aaaccgtata tatcaatatg 1380
aaaaagagaa agcagaaaca gaaaactcat gagagacaag cagtaagaaa cttcttttgg 1440
agaaacaaca gaccagatct ttactcacia ctcatgctag gaggccagtc ctgacattac 1500
cttatgttga aaatcttacc aatagtctgt gtcaacagaa tacttatttt agaagaaaaa 1560
ttcatgattt cttcctgaag cctgggcgac agagcgagac tctgtctcaa aaaaaaaaaa 1620
aaaaaaaaaa agaaagaaat gcctgtgctt acttcgcttc ccagg 1665

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<210> 179

<211> 179

<212> PRT

<213> Homo sapien

<400> 179

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Ala Asn Phe Gln Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro
1      5      10      15
Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys
20     25     30
Asn Glu Gln Thr Leu Arg Ala Asp Gln Met Phe Pro Ser Glu Ser Lys
35     40     45
Gln Lys Lys Val Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu Arg Glu
50     55     60
Thr Val Ser Gln Lys Asp Val Cys Val Pro Lys Ala Thr His Gln Lys
65     70     75     80
Glu Met Asp Lys Ile Ser Gly Lys Leu Glu Asp Ser Thr Ser Leu Ser
85     90     95
Lys Ile Leu Asp Thr Val His Ser Cys Glu Arg Ala Arg Glu Leu Gln
100    105    110
Lys Asp His Cys Glu Gln Arg Thr Gly Lys Met Glu Gln Met Lys Lys
115    120    125
Lys Phe Cys Val Leu Lys Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys
130    135    140
Ser Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser
145    150    155    160
Val Arg Phe Leu Thr Leu Met Lys Met Lys Ile Ile Ser Tyr Met Lys
165    170    175
Ile Ala Cys

```

<210> 180

<211> 1681

<212> DNA

<213> Homo sapien

<400> 180

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gatacagtca ttcttgtgaa agagcaaggg aacttcaaaa agatcactgt gaacaacgta      60
caggaaaaaat ggaacaaatg aaaaagaagt tttgtgtact gaaaaagaaa ctgtcagaag      120
caaaagaaat aaaatcacag ttagagaacc aaaaagttaa atgggaacaa gagctctgca      180
gtgtgagatt gactttaaac caagaagaag agaagagaag aaatgccgat atattaaatg      240
aaaaaattag ggaagaatta ggaagaatcg aagagcagca taggaaagag ttagaagtga      300
aacaacaact tgaacaggct ctcagaatac aagatataga attgaagagt gtagaaagta      360
atttgaatca ggtttctcac actcatgaaa atgaaaatta tctcttacat gaaaattgca      420
tggtgaaaaa ggaaattgcc atgctaaaac tggaatagc cacttgaaa caccaatacc      480
aggaaaaagg aataaaatc tttgaggaca ttaagatttt aaaagaaaag aatgctgaac      540
ttcagatgac cctaaaactg aaagaggaat cattaactaa aagggcctct caatatagt      600
ggcagcttaa agttctgata gctgagaaca caatgctcac ttctaaattg aaggaaaaac      660
aagacaaaga aatactagag gcagaaattg aatcacacca tcctagactg gcttctgctg      720
tacaagacca tgatcaaatt gtgacatcaa gaaaaagtca agaacctgct ttccacattg      780
caggagatgc ttgtttgcaa agaaaaatga atgttgatgt gagtagtacg atatatataca      840
atgaggtgct ccatcaacca ctttctgaag ctcaaaggaa atccaaaagc ctaaaaatta      900
atctcaatta tgccggagat gctctaagag aaaatacatt ggtttcagaa catgcacaaa      960
gagaccaacg tgaacacacag tgtcaaatga aggaagctga acacatgtat caaaacgaac     1020
aagataatgt gaacaaacac actgaacagc aggagtctct agatcagaaa ttatttcaac     1080
tacaagcaa aaatatgtgg cttcaacagc aattagttca tgcacataag aaagctgaca     1140
acaaaagcaa gataacaatt gatattcatt ttcttgagag gaaaatgcaa catcatctcc     1200
taaaagagaa aaatgaggag atattttaatt acaataacca tttaaaaaac cgtatatatc     1260
aatatgaaaa agagaaagca gaaacagaaa actcatgaga gacaagcagt aagaaacttc     1320
ttttggagaa acaacagacc agatctttac tcacaactca tgctaggagg ccagtcctag     1380
cattacctta tgttgaaaaa tcttaccat agtctgtgtc aacagaatac ttattttaga     1440
agaaaaattc atgatttctt cctgaagcct acagacataa aataacagtg tgaagaatta     1500
cttgttcacg aattgcataa aagctgcca ggatttccat ctaccctgga tgatgccgga     1560
gacatcattc aatccaacca gaatctcgct ctgtcactca ggctggagtg cagtgggcgc     1620
aatctcggtc cactgcaact ctgcctccca ggttcacgcc attctctggc acagcctccc     1680
g                                                                                   1681

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<210> 181

<211> 432

<212> PRT

<213> Homo sapien

<400> 181

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Asp Thr Val His Ser Cys Glu Arg Ala Arg Glu Leu Gln Lys Asp His
 1          5          10          15
Cys Glu Gln Arg Thr Gly Lys Met Glu Gln Met Lys Lys Lys Phe Cys
 20          25          30
Val Leu Lys Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu
 35          40          45
Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser Val Arg Leu
 50          55          60
Thr Leu Asn Gln Glu Glu Lys Arg Arg Asn Ala Asp Ile Leu Asn
 65          70          75          80
Glu Lys Ile Arg Glu Glu Leu Gly Arg Ile Glu Glu Gln His Arg Lys
 85          90          95
Glu Leu Glu Val Lys Gln Gln Leu Glu Gln Ala Leu Arg Ile Gln Asp
100          105          110
Ile Glu Leu Lys Ser Val Glu Ser Asn Leu Asn Gln Val Ser His Thr
115          120          125
His Glu Asn Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys
130          135          140
Glu Ile Ala Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr
145          150          155          160
Gln Glu Lys Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu
165          170          175
Lys Asn Ala Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu

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Thr	Lys	Arg	Ala	Ser	Gln	Tyr	Ser	Gly	Gln	Leu	Lys	Val	Leu	Ile	Ala
		195					200					205			
Glu	Asn	Thr	Met	Leu	Thr	Ser	Lys	Leu	Lys	Glu	Lys	Gln	Asp	Lys	Glu
	210					215					220				
Ile	Leu	Glu	Ala	Glu	Ile	Glu	Ser	His	His	Pro	Arg	Leu	Ala	Ser	Ala
225					230					235				240	
Val	Gln	Asp	His	Asp	Gln	Ile	Val	Thr	Ser	Arg	Lys	Ser	Gln	Glu	Pro
				245					250					255	
Ala	Phe	His	Ile	Ala	Gly	Asp	Ala	Cys	Leu	Gln	Arg	Lys	Met	Asn	Val
		260						265					270		
Asp	Val	Ser	Ser	Thr	Ile	Tyr	Asn	Asn	Glu	Val	Leu	His	Gln	Pro	Leu
	275						280					285			
Ser	Glu	Ala	Gln	Arg	Lys	Ser	Lys	Ser	Leu	Lys	Ile	Asn	Leu	Asn	Tyr
	290					295					300				
Ala	Gly	Asp	Ala	Leu	Arg	Glu	Asn	Thr	Leu	Val	Ser	Glu	His	Ala	Gln
305					310					315				320	
Arg	Asp	Gln	Arg	Glu	Thr	Gln	Cys	Gln	Met	Lys	Glu	Ala	Glu	His	Met
				325					330					335	
Tyr	Gln	Asn	Glu	Gln	Asp	Asn	Val	Asn	Lys	His	Thr	Glu	Gln	Gln	Glu
		340						345					350		
Ser	Leu	Asp	Gln	Lys	Leu	Phe	Gln	Leu	Gln	Ser	Lys	Asn	Met	Trp	Leu
	355					360						365			
Gln	Gln	Gln	Leu	Val	His	Ala	His	Lys	Lys	Ala	Asp	Asn	Lys	Ser	Lys
	370					375					380				
Ile	Thr	Ile	Asp	Ile	His	Phe	Leu	Glu	Arg	Lys	Met	Gln	His	His	Leu
385					390					395				400	
Leu	Lys	Glu	Lys	Asn	Glu	Glu	Ile	Phe	Asn	Tyr	Asn	Asn	His	Leu	Lys
			405					410					415		
Asn	Arg	Ile	Tyr	Gln	Tyr	Glu	Lys	Glu	Lys	Ala	Glu	Thr	Glu	Asn	Ser
			420					425					430		

<210> 182
 <211> 511
 <212> DNA
 <213> Homo sapiens

<400> 182
 gaagtttcat gaggttttagc ttttctgggc tggggagtgg agagaaagaa gttgcagggc 60
 ttacaggaaa tcccagagcc tgagggttttc toccagattt gagaactcta gattctgcat 120
 cattatcttt gagtctatat tctcttgggc tgtaagaaga tgaggaatgt aataggctctg 180
 cccaagcct ttcattgcctt ctgtaccaag cttgtttcct tgtgcatcct toccaggctc 240
 tggctgcccc ttattggaga atgtgatttc caagacaatc aatccacaag tgtctaagac 300
 tgaatacaaa gaacttcttc aagagttcat agacgacaat gccactacaa atgcatatga 360
 tgaattgaag gaatgttttc ttaaccaaac ggatgaaact ctgagcaatg ttgaggtggt 420
 tatgcaatta atatatgaca gcagtccttg tgatttattt taactttctg caagaccttt 480
 ggctcacaga actgcagggt atggtgagaa a 511

<210> 183
 <211> 260
 <212> DNA
 <213> Homo sapiens

<400> 183
 cacctcgcgg ttcagctcct ctgtcttggt gaagaacat tcctcggcat ccttgcggtt 60
 cttctctgcc atcttctcat actggtcacg catctcgttc agaatgcggc tcagggtccac 120
 gccagggtga gcgtccatct ccacattgac atctccacc accctggctc tcagggtcatt 180
 catctcctcc tcgtggttct tcttcaggta ggccagctcc tccttcaggc tctcaatctg 240
 catctccagg tcagctcttg 260

<210> 184
 <211> 461

<212> DNA
<213> Homo sapiens

<400> 184
gtctgatggg agaccaaaga atttgcaagt ggatgggttg gtatcactgt aaataaaaag 60
agggcctttt ctatgtgtat gactgttact tgaccttctt tgaaaagcat tcccaaaatg 120
ctctatttta gatagattaa cattaaccaa cataattttt tttagatcga gtcagcataa 180
atttctaagt cagcctctag tcgtggttca tctctttcac ctgcatttta tttgggtgtt 240
gtctgaagaa aggaaagagg aaagcaaata cgaattgtac tatttgtacc aaatctttgg 300
gattcattgg caaataatth cagtgtgggtg tattattaaa tagaaaaaaa aaattttgtt 360
tcctaggttg aaggctaat tgataccgtt tgacttatga tgaccattta tgcactttca 420
aatgaatttg ctttcaaaat aaatgaagag cagacctcgg c 461

<210> 185
<211> 531
<212> DNA
<213> Homo sapiens

<400> 185
tctgatttta ttctcttctc aaaaaaagtt atttacagaa ggtatatatc aacaatctga 60
caggcagtga acttgacatg attagctggc atgatttttt cttttttttc ccccaaacat 120
tgtttttgtg gccttgaatt ttaagacaaa tattctacac ggcatattgc acaggatgga 180
tggcaaaaaa aagtttaaaa acaaaaaccc ttaacggaac tgccttaaaa aggcagacgt 240
cctagtgcct gtcatgttat attaaacata catacacaca atctttttgc ttattataat 300
acagacttaa atgtacaaag atgttttcca cttttttcaa tttttaaaca caacagctat 360
aaacctgaac acatattgcta tcatcatgcc ataagactaa aacaattata tttagcgaca 420
agttagaaagg attaaatagt caaatacaag aatgaaaaac gcagtacata gtgtcgcgaa 480
ctcaaatcgg catttagata gatccagtgg tttaaacggc acgtttttgc t 531

<210> 186
<211> 441
<212> DNA
<213> Homo sapiens

<400> 186
cattcctttt ctgcggttg ggtttctctg tgtcagcgag cctcgggtaca ctgatttccg 60
atcaaaaagaa tcatcatctt taccttgact tttcaggga ttactgaact ttcttctcag 120
aagatagggc acagccattg ccttggcctc acttgaaggg tctgcatttg ggtcctctgg 180
tctcttgcca agttttccaa ccactcgagg gagaaatata gggagggttg acttcctccg 240
gggctttccc gagggcttca ccgtgagccc tgcggccctc agggctgcaa tcctggattc 300
aatgtctgaa acctcgctct ctgcctgctg gacttctgag gccgtcactg ccactctgtc 360
ctccagctct gacagctcct catctgtggt cctgttgtac tggacggggg ccccagggtc 420
ctgggggctt ttttctgtc t 441

<210> 187
<211> 371
<212> DNA
<213> Homo sapiens

<400> 187
aaaagtgaat gagtaactat tatattgttg gcaataataa gttgcaaaat catcaggctg 60
caggctgctg atgggtgagag tgaactctgt cccagatcca ctgccgctga accttgatgg 120
gacccagatg tctaaactag acgccttatg gatcaggagc tttggggctt tccctggtt 180
ctgttgatac caggccaacc aactactaac actctgactg gcccggaag tgatgggtgac 240
tctgtctcct acagttgcag acagggtgga aggagactgg gtcactctgga tgtcacattt 300
ggcactctgg agccagagca gcaggagccc caggagctga gcggggaccc tcatgtccat 360
gctgagtcct g 371

<210> 188
<211> 226
<212> DNA
<213> Homo sapiens

<400> 188
 ggtatataaa ttgagatgcc cccccaggcc agcaaatggt cctttttgtt caaagtctat 60
 ttttattcct tgataattttt cttttttttt tttttgtgga tggggacttg tgaatttttc 120
 taaaggtgct atttaacatg ggaggagagc gtgtgagggt ccagcccagc ccgctgctca 180
 ctttccaccc tctctccacc tgcctctggc ttctcaggac ctgccc 226

<210> 189
 <211> 391
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(391)
 <223> n=A,T,C or G

<400> 189
 tgggtgaagt ttattctggt ttcacatcta ggttggtggg ganagtgata gacaaagttc 60
 tggattctgg gcatcgctgg cgcattgctt taatcctact tgggagggtg anacaggaga 120
 cctcgccgcg naccacgcta agggcggaatt ctgcanatat ccatcacact ggccggccgct 180
 cgagcatgca tctanagggc ccaattcncc ctatagttag ncgtattaca attcactggc 240
 cgctggttta caacgtcgtg actgggaaaa ccctggcggt acccaactta atcgcccttc 300
 agcacatccc cctttcncca gctggcctta tancgaagag gcccgcaccc atcgcccttc 360
 ccaacanttg cgcagcctga atggcggaatg g 391

<210> 190
 <211> 501
 <212> DNA
 <213> Homo sapiens

<400> 190
 catcttgagg tttttgagct gtttccgctt cttctcatcc cggtcactgt caccctcatt 60
 actggaggag ctggcagagg cgttgctgtc aaactcctct gccacatctt cctcctcttc 120
 acctgggttg aatgactcat cgttttcttc tcctgagtca tcgctgctgt cattggcatt 180
 ctctcccgg atcttgccct cctccttcct cctctccaag taggcattcat gctggtcctc 240
 atcagagtca gcatattcat cgtagcttgg gttcatgccc tctttcaatc ctcggttttt 300
 gatgttgagc tttttcgcgt tgacaaaatc aaacagtttc ccgtactcct ccctctcaat 360
 gctgctgaag gtatactgag tgcctgctt ggtctcaatt tcaaagtcaa aggaacgagt 420
 agtagtggtg ccacgagcaa agttgacaaa ggagatctca tcgaagcgga tgtgcacagg 480
 tggcttggtg acgtagatga a 501

<210> 191
 <211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (49)
 <223> n=A,T,C or G

<400> 191
 ggaaaaactg tgaaaaatat atctgaattt attaagtaca gtataaaaana gggttgtggc 60
 aacagaaaagt aaaaactaac atggattgct ataaatatgc tgaagcctag ttgttcaaat 120
 gatacaattc tctcatgcta ctctaaagtt tataaagaaa aaggatttac actttacaca 180
 ctgtacacaa aaggaatacc ttctgagagc cagggagtgg ggaaagggga aggagacttg 240
 a 241

<210> 192
 <211> 271
 <212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(271)

<223> n=A,T,C or G

<400> 192

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tggtcntgga ttcacanata aantanatcg actaaaactg gcagaaattg tgaagcaggt 60
gatagaagan caaaccacgt cccacgaatc ccaataatga cagcttcaga ctttgctttt 120
ttaacaattt gaaaaattat tctttaatgt ataaagtaat tttatgtaa ttaataaatc 180
ataatttcat ttccacattg attaaagctg ctgtatagat ttagggngca ggacttaata 240
atagnggaaa tgaaattatg atttattaat c 271

```

<210> 193

<211> 351

<212> DNA

<213> Homo sapiens

<400> 193

```

agtcgaggcg ctgatcccta aaatggcgaa catgtgtttt catcatttca gccaaagtcc 60
taacttcctg tgcttttct atcacctcga gaagtaatta tcagttggtt tggatttttg 120
gaccaccgtt cagtcatttt gggttgccgt gctcccaaaa cattttaat gaaagtattg 180
gcattcaaaa agacagcaga caaaatgaaa gaaaatgaga gcagaaagta agcatttcca 240
gcctatctaa tttctttagt tttctatttg cctccagtc agtccatttc ctaatgtata 300
ccagcctact gtactattta aaatgctcaa tttcagcacc gatggacctg c 351

```

<210> 194

<211> 311

<212> DNA

<213> Homo sapiens

<400> 194

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ctgagacaca gaggccact gcgaggggga cagtggcggg gggactgacc tgctgacagt 60
caccctccct ctgctgggat gaggtccagg agccaactaa aacaatggca gaggagacat 120
ctctggtgtt cccaccacc tagatgaaa tccacagcac agacctctac cgtgtttctc 180
ttccatccct aaaccacttc cttaaaatgt ttggatttgc aaagccaatt tggggcctgt 240
ggagcctggg gttggatagg gccatggctg gtccccacc atacctcccc tccacatcac 300
tgacacagac c 311

```

<210> 195

<211> 381

<212> DNA

<213> Homo sapiens

<400> 195

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tgtcagagtg gcaactggtg aagttccagg aaccctgaac tgtaagggtt cttcatcagt 60
gccaacagga tgacatgaaa tgatgtactc agaagtgtcc tggaatgggg cccatgagat 120
ggttgtctga gagagagctt cttgtcctgt ctttttcctt ccaatcaggg gctcgtcttt 180
ctgattattc ttcagggcaa tgacataaat tgtatattcg gttcccgggt ccaggccagt 240
aatagtagcc tctgtgacac cagggcgggg ccgagggacc acttctctgg gaggagacc 300
aggcttctca tacttgatga tgtagccggt aatcctggca cgtggcgggt gccatgatac 360
cagcagggaa ttgggtgtgg t 381

```

<210> 196

<211> 401

<212> DNA

<213> Homo sapiens

<400> 196

```

cacaacaag aggagcacca gacctcctct tggcttcgag atggcttcgc cacaccaaga 60
gcccaaacct ggagacctga ttgagatctt ccgccttggc tatgagcact gggccctgta 120

```

55

```

tataggagat ggctacgtga tccatctggc tcctccaagt gagtaccocg gggctggctc 180
ctccagtgtc ttctcagtc tgagcaacag tgcagaggtg aaacgggagc gcctggaaga 240
tgtgggtggga ggctgttgct atcgggtcaa caacagcttg gaccatgagt accaaccacg 300
gcccggtggag gtgatcacca gttctgcgaa ggagatgggt ggtcagaaga tgaagtacag 360
tattgtgagc aggaactgtg agcactttgt caccagacc t 401

```

<210> 197
 <211> 471
 <212> DNA
 <213> Homo sapiens

```

<400> 197
ctgtaatgat gtgagcaggg agccttcctc cctgggccac ctgcagagag ctttcccacc 60
aactttgtac cttgattgcc ttacaaagt atttgtttac aaacagcgac catataaaag 120
cctcctgccc caaagcttgt gggcacatgg gcacatacag actcacatac agacacacac 180
atataatgtac agacatgtac tctcacacac acaggcacca gcatacacac gtttttctag 240
gtacagctcc caggaacagc taggtgggaa agtcccatca ctgagggagc ctaaccatgt 300
ccctgaacaa aaattgggca ctcatctatt ctttttctct tgtgtcccta ctcattgaaa 360
ccaaactctg gaaaggaccc aatgtaccag tatttatacc tctagtgaag cacagagaga 420
ggaagagagc tgcttaact cacacaacaa tgaactgcag acacagacct g 471

```

<210> 198
 <211> 201
 <212> DNA
 <213> Homo sapiens

```

<400> 198
ggtccattga ggctctgtcg gccatgccc cagttcgaag ctttgccaac gaggagggcg 60
aagcccagaa gtttagggaa aagctgcaag aaataaagac actcaaccag aaggaggctg 120
tgccctatgc agtcaactcc tggaccacta gtatttcagg tatgctgctg aaagtgggaa 180
tcctctacat tggtaggcag a 201

```

<210> 199
 <211> 551
 <212> DNA
 <213> Homo sapiens

```

<400> 199
tctggcacag atcttcaccc acacggcggt ccacgtgctg atcatcttcc gggctctacc 60
gggcctggaa cacaccatct tccccatgag cccggtgccc agtctggtga cttccatctt 120
ggcccttgcc cttatgtccc agttatgacc cctgacttca actctggctc ttaccctgta 180
actccagtcc atctctgaca tttttaacac ccggccttgt gaccgtggac atagctcctg 240
acctcgattc ccatcttgag ccagtggtta gtccatgaga tcatgacctg actcctggtc 300
tccaaccttg tgatcctaatt tctgggacct caatcctagc ctctgaactt gggaccttgg 360
agctcctgac cttagtctcg accgctaccc ttgattctga cctttgatcc tgtaacttag 420
gggtggcccc tgaccttatt actgtcattt agctccttga ccttgccact tcaatcctgg 480
ctttatgacc tcctactctc aattttaact ttaaccaaat gaccaaattt gtgacactaa 540
atgaccacaa t 551

```

<210> 200
 <211> 211
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(211)
 <223> n=A,T,C or G

```

<400> 200
cagctcanag ggcgacatgc ccctacaagt tggcanaagn ggctgccact gctgggtttg 60
tgtaagagag gctgctgnca ccattacctg cagaaacctt ctcatagggg ctacgatcgg 120

```


56

tactgctagg gggcacatag cgcccatggg tgtggtaggt ggggnactcn ntataggat 180
 ggtaggtatc ccgggctgga aanatggnca g 211

<210> 201
 <211> 111
 <212> DNA
 <213> Homo sapiens

<400> 201
 ccagtgaag gaaacaaaac tggcagtttg tccatttgaa tatcagacct agtttcttct 60
 taatttccac actatttctc ccatattcct taaacttctt ggcatccacc t 111

<210> 202
 <211> 331
 <212> DNA
 <213> Homo sapiens

<400> 202
 tgaaaaata gaataaccagg tgggtcccaaa tgtttgaagt tctttgaaca gaaagagaga 60
 ggagagagag agagaggaaa attccctaac ccttggttta aagacaatat tcattttattg 120
 ctcaaagtat gcttttaagg gaggacagtg gaataaaaata aacttttttt ttctccctac 180
 aatacataga aggggttatca aaccactcaa gtttcaaaat ctttccaggg tccaatatca 240
 ctttttttct ttcggttcaa tgaaaagcta aatgtaataa tactaattat agataaaatt 300
 ttattttact ttttaaaaat ttgtccagac c 331

<210> 203
 <211> 491
 <212> DNA
 <213> Homo sapiens

<400> 203
 agtcacccag tctacttagt acctgggtgc tgccctctgac cttttcagct tgataccctg 60
 ggcttttagtg taaccaataa atctgtagtg accttacctg tattccctgt gctatcctgt 120
 gggaaggtag gaatgggcta agtatgatga atgtataggt tagggatctt ttgggttttaa 180
 atcacagaaa acctaattca aactggctta aaataaaaag gattttattgg ttcatgtaac 240
 tagaaagtcc ataggttagtg ctggctccag gtgaagactt gaccagtag ttcagtatgt 300
 ctctaaatac cggactgact tttttctcac tgttgcatct tctgtaggac catttaagtc 360
 tgggccactt aatggctgcc agcattccta agattacact tttccccatt tatgtccaat 420
 cagaaaaaga aggcattctt gtaccagaaa tctcagcaaa agccctaata ttcacactga 480
 ttaggacctg c 491

<210> 204
 <211> 361
 <212> DNA
 <213> Homo sapiens

<400> 204
 tcccttcctc ccccatgtga taaatgggtc cagggtgat caaagaactc tgactgcaga 60
 actgccgctc tcagtggaca gggcatctgt tatcctgaga cctgtggcag acacgtcttg 120
 ttttcatttg atttttgtta agagtgcagt attgcagagt cttagaggaat ttttgtttcc 180
 ttgattaaca tgattttcct ggttggtaca tccaggcat ggcagtggcc tcagccttaa 240
 acttttggtc ctactccac cctcagcgaa ctgggcagca cggggagggt ttggctaccc 300
 ctgcccattc ctgagccagg taccaccatt gtaaggaaac actttcagaa attcagacct 360
 c 361

<210> 205
 <211> 471
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature

57

<222> (2)
<223> n=A,T,C or G
<221> misc_feature
<222> (3)
<223> n=A,T,C or G

<400> 205
cnngtacagt tcttctctgga tggccgacac agatcctggg gaaaggcaat cctggcactg 60
ctctgaaacc agagctcctc ctccctcccc gggcaggggt gagctgagaa gggctgctct 120
agcgtttgga ctccacctcc atacacctga tatattgata gggcaggtcc ctgctatggg 180
ccactgttct gggcagtata gtatgcttga cagcatcctt ggcatctatc caccagatcc 240
cagagcacc cgtactagct gtgacaacat cctccaaaca ttgcaaaatt tcccctggga 300
ggcaagattg cctcagatgg gagaatcacg ctctagggaa atctgctggt atgagaaccc 360
caactcccca ctccactgag cctccagatg gcgagcaggc tgcagctcca gcacagacac 420
gaagctccct ccagccactg acggtccatg gctgggggta cccaggacct c 471

<210> 206
<211> 261
<212> DNA
<213> Homo sapiens

<400> 206
tagagtattt agagtctctga gataacaagg aatccaggca tccttttagac agtcttctgt 60
tgtcctttct tcccaatcag agattttgtg atgtgtggaa tgacaccacc accagcaatt 120
gtagccttga tgagagaatc caattcttca tctccacgaa tagcaagttg caagtgcga 180
ggggaataac gctttacctt taagtctttt gatgcatttc ctgccagttc aagtacctct 240
gcggtgaggt actccaggat g 261

<210> 207
<211> 361
<212> DNA
<213> Homo sapiens

<400> 207
gctctccggg agcttgaaga agaaactggc tacaaagggg acattgccga atgttctcca 60
gcggtctgta tggaccagg cttgtcaaac tgtactatac acatcgtgac agtcaccatt 120
aacggagatg atgccgaaaa cgcaaggccg aagccaaagc caggggatgg agagtttgtg 180
gaagtcattt ctttacccaa gaatgacctg ctgcagagac ttgatgctct ggtagctgaa 240
gaacatctca cagtgagcgc caggggtctat tcctacgctc tagcactgaa acatgcaaatt 300
gcaaagccat ttgaagtgcc cttcttgaaa ttttaagccc aaatatgaca ctggacctgc 360
c 361

<210> 208
<211> 381
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(381)
<223> n=A,T,C or G

<400> 208
agaggagatn tttgccatgc ctgaatnctt tcctatncca ccctancact taacatatta 60
cttagtctgc tttgntaaaa gcaagtatta ccttnaactt gnctcttact ctttgccctt 120
tagctaacta ataaagnttg atntaggcat tattatataa ttctgagtca ttcatggat 180
ctctcatggt tgatgtattt tncaaactaa gatctatgat agtttttttt ccanagttcc 240
attaaatcat ttatttcctt tactttctca cctctgtnga aacatttaga aactggattt 300
gggaacccan ttttggaata ccagattcat agtcatgaaa atggaaactt ncatattctg 360
tttttgaaaa gatgtggacc t 381

<210> 209

<211> 231
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (83)
<223> n=A,T,C or G

<400> 209
gtggagagca agtgatttat taaagcaaga cggtgaaacc ttacattct gcagtgaaga 60
tcagggtgtc attgaaagac agnggaaacc aggatgaaag tttttacatg tcacacacta 120
catttcttca atattttcac caggacttcc gcaatgaggc ttcgtttctg aaggacatc 180
tgatccgtgc atctcttcac tccaaacttg gctgcaacag cttccacctg c 231

<210> 210
<211> 371
<212> DNA
<213> Homo sapiens

<400> 210
tccatcctgg ttttgcagag atcaggttgt tgacagttcc tgggtgaccc acagctaccc 60
atgtcagtta tctccactaa catatccaag aatctttgta ggacaatttc tccaactgca 120
agggttttta ggtagaactc ttcttttaag gcaattagcc cattgccaaa aggttttact 180
gtcttaaaagc tgtctttctg agatctaatt ccaaggactt ctccacagct aagtgagatg 240
cctcacacca ttaggtgatg ctttgacag aacagagtat tttcatcttg tgtttaaagc 300
aattccttgg cttcggtcc tcaccacttt ctatgccagt ctcccattta tgtccctagt 360
aatgcctatg c 371

<210> 211
<211> 471
<212> DNA
<213> Homo sapiens

<400> 211
tttattttta aagaaaaaaa ttaaaataga gccacaacat gcaattaaga aaaaaaagt 60
attgagacac aaggggacct acatgttctg gtctaagaag catgcaagta ttacaaagca 120
ttccagatac agtatgacag aggaacagtg aacaagcatt ggaacgatgc tctttctttc 180
agaaacggga agtctaacag ttatgttttc acaatggtag tgattaaacc atctttattt 240
ttaaggaatt ttataggaag aatttttagca ccattcattaa aggaaaaata ataatacctt 300
tttagccctg cctatctcca gtcttggaat aataacagaa gcatagcacc tttcagtatc 360
taaaatataa acaagaatag taagtccatc ccagcttcta gagatgaggt agctcatgct 420
aagaaatgtt gggtcatttt toctatgaaa gttcaaaggc caaatggtca c 471

<210> 212
<211> 401
<212> DNA
<213> Homo sapiens

<400> 212
tggcctgtct ccttcacata gtccatatca ccacaaatca cacaacaaaa gggagaggat 60
atattttggg ttcaaaaaaa gtaaaaagat aatgtagctg catttctttg gttatttttg 120
gccccaaata tttctcatc tttttgtgt tgcattgat ggtggtgaca tggacttggt 180
tatagaggac aggtcagctc tctggctcgg tgatctacat tctgaagttg tctgaaaatg 240
tcttcatgat taaattcagc cttaaagttt tgccgggaac actgcagaga caatgctgtg 300
agtttccaac ctgagcccat ctgctggcag agaaggtcta gtttgtccat caccattatg 360
atatcaggac tggttacttg gtttaaggag ggtctacctc g 401

<210> 213
<211> 461
<212> DNA
<213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(461)
 <223> n=A,T,C or G

<400> 213
 tgtgaagcat acataaataa atgaagtaag ccatactgat ttaattttatt ggatgtttatt 60
 ttccctaaga cctgaaaatg aacatagtat gctagttatt ttccagtgtt agcctttttac 120
 ttccctcaca caatttgga tcatataata taggtacttt gtccctgatt aaataatgtg 180
 acggatagaa tgcatacaagt gtttattatg aaaagagtgg aaaagtatat agctttttanc 240
 aaaagggtgtt tgccatttct aagaaatgag cgaatatata gaaatagtgn gggcattttct 300
 tcctgttagg tggagtgtat gtgttgacat ttctcccat ctcttccac tctgtttnt 360
 cccattatt tgaataaagt gactgctgaa nangactttg aatccttat cacttaattt 420
 aatgttttaa gaaaaaccta taatggaaag tgagactcct t 461

<210> 214
 <211> 181
 <212> DNA
 <213> Homo sapiens

<400> 214
 cctgagcttc tactcctttc ccttaagatt cctccaaagc accagctcca taaaatcctt 60
 cagctcccca gaccacacc aagaaccca catgttaatt ggatcagcca aatctacaag 120
 cagataagtc ctaaggagaa tgccgaagcg tttttcttct tcctcaagcc tagcatgaga 180
 c 181

<210> 215
 <211> 581
 <212> DNA
 <213> Homo sapiens

<400> 215
 ctgctttaag aatggttttc caccttttcc ccctaacttc taccaatcag acacatttta 60
 ttattttaaat ctgcacctct ctctatttta ttgtccaggg gcacgatgtg acatatctgc 120
 agtcccagca cagtgggaca aaaagaattt agaccccaa agtgtcctcg gcatggatct 180
 tgaacagaac cagtatctgt catggaactg aacattcatc gatggctctc atgtattcat 240
 ttattcactt gtccattcaa gtatttattg aatacctgcc tcaagctaga gagaaaagag 300
 agtgcgcttt ggaaatttat tccagttttc agcctacagc agattatcag ctcggtgact 360
 ttcttttctg ccaccattta ggtgatgggtg ttgtattcag agatggctga atttctattc 420
 ttagctttatt gtgactgttt cagatctagt ttgggaacag attagaggcc attgtcctct 480
 gtccctgatca ggtggcctgg ctgtttcttt ggatccctct gtcccagagc caccagaac 540
 cctgactcct gagaatcaag aaaacaccca gaaaggacct c 581

<210> 216
 <211> 281
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(281)
 <223> n=A,T,C or G

<400> 216
 ccgatgtcct gcttctgtgg accaggggct cctctgnngg tggcctcaac cacggctgag 60
 atccctagaa gtccaggagc tgtggggaag agaagcactt agggccagcc agccgggcac 120
 cccacttgcc gccccgaccc acgctcagc accagacctg ccngggcggc cgctcnaaag 180
 ggcaatttct gcagatatcc atcacactgg cggacgctcg agcatgcatc tagagggcc 240
 aattcaccct atantgagtc gtattacaat tcaactggccg t 281

<210> 217

<211> 356
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(356)
<223> n=A,T,C or G

<400> 217
atagcagggt tcaacaattg tcttgtagtt tgnagtaaaa agacataaga aagagaaggt 60
gtggttttgca gcaatccgta gttggtttct caccataccc tgcagttctg tgagccaaag 120
gtcttgcaga aagttaaaat aaatcacaaa gactgctgtc atatattaat tgcataaaca 180
cctcaacatt gctcagagtt tcatccgttt ggtaagaaa acattccttc aattcatcta 240
tggcatttgt agtggcattg tcgtctatga actcttgaag aagttctttg tattcagtct 300
tagacacttg tggattgatt gncttggaat tcacattctc caataaggga cctcgg 356

<210> 218
<211> 321
<212> DNA
<213> Homo sapiens

<400> 218
ttgtccatcg ggagaaaggt gtttgtcagt tgtttcataa accagattga ggaggacaaa 60
ctgctctgcc aatttctgga tttctttatt ttcagcaaac actttcttta aagcttgact 120
gtgtgggcac tcatccaagt gatgaataat catcaagggt ttgttgcttg tcttggattt 180
atatagagct tcttcatatg tctgagtcga gatgagttgg tcaccccaac ctctggagag 240
ggctctgggc agtttgggtc gagagtcctt tgtgtccttt ttggctccag gtttgactgt 300
ggtatctctg gacctgcctg g 321

<210> 219
<211> 271
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (41)
<223> n=A,T,C or G

<400> 219
ccggttaggt ccacgcgggg gcagtggagg cacaggetca nggtggccgg gctacctggc 60
accctatggc ttacaaagta gagttggccc agtttccttc cacctgaggg gagcactctg 120
actcctaaca gtcttccttg ccctgccatc atctgggggtg gctggctgtc aagaaaggcc 180
gggcatgctt tctaaacaca gccacaggag gcttgtaggg catcttccag gtggggaaac 240
agtcttagat aagtaagggt acttgtctaa g 271

<210> 220
<211> 351
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(351)
<223> n=A,T,C or G

<400> 220
gtcctacgac gaggaccagc ttttcttctt cnacttttcc canaacactc ggggtgcctcg 60
cctgcccga tttgctgact gggctcagga acaggagat gctcctgcca ttttatttga 120
caaagagttc tgcgagtgga tgatccagca aatagggccaa aaacttgatg ggaaaatccc 180
gggtgtccaga gggtttcccta tcgtgaagt gttcacgctg aagcccctgg agtttgga 240

61

gccaacact ttggtctgtt ttgtcagtaa tctcttccca cccatgctga cagtgaactg 300
 gtagcatcat tccgtccctg tgggaaggatt tgggcctact tttgtctcag a 351

<210> 221
 <211> 371
 <212> DNA
 <213> Homo sapiens

<400> 221
 gtctgcagaa gcgtgtctga ggtgtccggt ggaggtggca gccgagctct gggactaatc 60
 accgtgctgg ggacggcacc gcgtcaggat gcaggcagat ccctgcagaa gtgtctaaaa 120
 ttcacactcc tcttctggag ggacgtcgat ggtattagga tagaagcacc aggggacccc 180
 acgaacggtg tcgtcgaaac agcagccctt atttgcacac tgggagggcg tgacaccagg 240
 aaaaccacaa ttctgtcttt cacggggggc cactgtacac gtctctgtct gggcctcggc 300
 cagggtgccg agggccagca tggacaccag gaccagggcg cagatcacct tgttctccat 360
 ggtggacctc g 371

<210> 222
 <211> 471
 <212> DNA
 <213> Homo sapiens

<400> 222
 gtccatgttc catcattaat gttccaacat caccagggac acaaagctgc aaaaatgaga 60
 agggaaataa ggtagagaa aggatccggg caatcttaag gactgaggaa gacatgttcc 120
 ccaacccttg aactcacaaa ccctgaagct caaggattgc atccttcctc caaatctcac 180
 tcaacataat aagtgcagaa caacatgcca aagcactgta tgaagcacta gggacaaaga 240
 caaggtcaaa atccttgtta ccaaatttaa tggattgta atgcagtgtt aacacaggac 300
 agtaacagaa caccaagaa ccaaacagaa gagggtaggg ataagcataa atgaagtaac 360
 atgaaataaa cttccaaatg gaaaacttgt ccataccccc agggcaagtc aactacagtc 420
 tcccaaagga cataaattcc acttagggca cactagacag aaaacaatat t 471

<210> 223
 <211> 411
 <212> DNA
 <213> Homo sapiens

<400> 223
 agttgtctca caatgacaca caaatcccgt taaataaatt ataaacaagg gtcaattcaa 60
 atttgaagta atgttttagt aaggagagat tagaagacaa caggcatagc aaatgacata 120
 agctaccgat taactaatcg gaacatgtaa aacagttaca aaaataaacg aactctctc 180
 ttgtcctaca atgaaagccc tcatgtgcag tagagatgca gtttcatcaa agaacaaca 240
 tccttgcaaa tgggtgtgac gcggttccag atgtggattt ggcaaaacct catttaagta 300
 aaaggttagc agagcaaaagt gcggtgcttt agctgctgct tgtgccgctg tggcgtcggg 360
 gaggtcctcg cctgagcttc cttccccagc tttgctgctt gagaggaacc a 411

<210> 224
 <211> 321
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (31)
 <223> n=A,T,C or G

<400> 224
 ggtctgaagt ttgataacaa agaaatatat ntaagacaaa aatagacaag agttaacaat 60
 aaaaacacaa ctatctgttg acataacata tggaaacttt ttgtcagaaa gctacatctt 120
 cttaatctga ttgtccaaat cattaaaata tggatgattc agtgccattt tgccagaaat 180
 tcgttttggc ggatcataga ttaacatttt cgagagcaaa tccaagccat tttcatccaa 240
 gtttttgaca tgggatgcta ggcttctctg tttccatttg ggaaatgtat tcttatagtc 300

ctgtaaagat tccacttctg g

321

<210> 225
<211> 251
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (34)
<223> n=A,T,C or G

<400> 225
atgtctgggg aaagagttca ttggcaaaaag tgnctccca agaatgggtt acaccaagca 60
gagaggacat gtcactgaat ggggaaaggg aacccccgta tccacagtca ctgtaagcat 120
ccagtaggca ggaagatggc tttgggcagt ggctggatga aagcagattt gagataccca 180
gctccggaac gaggtcatct tctacaggtt cttccttcac tgagacaatg aattcagggg 240
gatcattctc t 251

<210> 226
<211> 331
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (1)...(331)
<223> n=A,T,C or G

<400> 226
gttaggtccc agggcccccg ccaagnngtt accnnmntna ccaactcctga cccaaaaatc 60
aggcatggca ttaaaacggt gcaaattcct ttactgttat cccccccacc accaggacca 120
tgtaggggtc agtctttact ccctaaccog tttcccgaaa aagggtgctac ctcctttcca 180
gacagatgag agagggcagg acttcaggct ggatccacca ctgggctctc cctccccag 240
cctggagcac gggaggggag gtgacggctg gtgactgatg gatgggtagt gggctgagaa 300
gaggggacta ggaagggcta ttccaggctc a 331

<210> 227
<211> 391
<212> DNA
<213> Homo sapiens

<400> 227
aggtctgccc ttgaagtata ggaaggaatc atagttggag gacttctgca ttatttgttg 60
gctgaagcta gaagtgaac cccctcctga tttctgcagc aagatgaact gccttatccc 120
cagcccgagc gaatgttcat atctgagcaa tcaatgggca ctgtgttcaa ccacgccatt 180
ttcaagattg gtcctttaa ccaccacaa ggcaccagct ctgggagaag ctgcagggag 240
aagagaacaa agccctcgct gtgatcagga tgggtgtctc atacctttc tctgggggtca 300
ttccaggtat gagacagagt tgaacctgcg catgagcgtg gaggccgaca tcaacggcct 360
gcgcaggggtg ctggatgagc tgacctgga c 391

<210> 228
<211> 391
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (35)
<223> n=A,T,C or G

<400> 228

63

```

gttgtccata gccacctcct gggatagaag ctttntagtt catagtccga ttagtgtgtc 60
cttaggacat aggtccagcc ctacagatta gctgggtgaa gaaggcaagt gtctcgacag 120
ggcttagtct ccaccctcag gcatggaacc attcaggggtg aagcctggga tgtgggcaca 180
ggagactcag gctgatataa aaataacaaa atcagtaata aaaaaattat aaaacctgtt 240
gcttgctctga atagatttga gcaacagtct tgcttttggt aaaaatcctgg agccgttaag 300
tcctgaatat tcttctggac atcattgctg gctggagaaa ggagccccag gcccggtcgt 360
gctgacatct gtcaggtttg gaagtctcat c 391

```

```

<210> 229
<211> 341
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (202)
<223> n=A,T,C or G

```

```

<400> 229
gtccatggct tctcaccag acagtctttc tgggcaactt ggggaagccc ctgttctgct 60
caagtctcac cccatggaag aggtggggga agggggcctt ggtttttcag gaagacgggt 120
tgagagcac gagtcactac aaagcagtaa aagtgaatgg tgtctccagg ggctgggtcc 180
agaacaccgc ggagagcccc anccataaag gtgtgttccg cctctggcct gcaggaatct 240
ctttgaatct ctttgattgg tggctccaag agcaatggga agtcaacagc caggaggctg 300
gactgggttc cctgggaccc cgaggtccca gaggtgctg g 341

```

```

<210> 230
<211> 511
<212> DNA
<213> Homo sapiens

```

```

<400> 230
gtccaagcca aggaaaccat tcccttacag gagacctccc tgtacacaca ggaccgcctg 60
gggctaaagg aaatggacaa tgcaggacag ctagtgttcc tggctacaga aggggaccat 120
cttcagttgt ctgaagaatg gttttatgcc cacatcatac cattccttgg atgaaaccg 180
tatagttcac aatagagctc agggagcccc taactcttcc aaaccacatg ggagacagtt 240
tccttcacgc ccaagcctga gctcagatcc agcttgcaac taatccttct atcatctaac 300
atgccctact tggaaagatc taagatctga atcttatcct ttgccatctt ctgttaccat 360
atgggtgttga atgcaagttt aattaccatg gagattgttt tacaaaacttt tgatgtggtc 420
aagttcagtt ttagaaaagg gagtctgttc cagatcagtg ccagaactgt gccagggccc 480
aaaggagaca actaactaaa gtagtgagat a 511

```

```

<210> 231
<211> 311
<212> DNA
<213> Homo sapiens

```

```

<400> 231
ggccaagta agctgtgggc aggcaagccc ttcggtcacc tgttggttac acagaccctt 60
cccctcgtgt cagctcagga agctcgagga ccccgaccaa cacttgagga ggtccctgct 120
agttagcgcc ccaccgcgt ggagttcgta ccgcttcctt agaacttcta cagaagccaa 180
gtccctgga gccctgttgg cagctctagc tttgcagtcg tgtaattggc ccaagtcat 240
gtttttctcg cctcactttc caccaagtgt ctagagtcac gtgagcctcg tgtcatctcc 300
gggggtggacc t 311

```

```

<210> 232
<211> 351
<212> DNA
<213> Homo sapiens

```

```

<400> 232
tcgttttagct aataatccct tccttgatga tacactccaa cttcttggtt ttctttat 60

```


64

```

ctaaaaagcg gttctgtaac tctcaatcca gagatgttaa aaatgtttct aggcacggta 120
ttagtaaatc aagtaaattt catgtcctct taaaggacaa acttccagag atttgaatat 180
aaatttttat atgtgttatt gattgtcgtg taacaaatgg cccccacaaa ttagtagctt 240
aaaatagcat ttatgatgtc actgttttct ttgccttttc attaatgttc tgtacagacc 300
tatgtaaaaca acttttgtat atgcatatag gatagctttt ttgagggtat a 351

```

```

<210> 233
<211> 511
<212> DNA
<213> Homo sapiens

```

```

<400> 233
aggtctggat gtaaggatgg atgctctcta tacatgctgg gttggggatg ctgggactgc 60
acagccaccc ccagtatgcc gctccaggac tctgggacta gggcgccaaa gtgtgcaaat 120
gaaaatacag gatacccagg gaactttgaa tttcagattg tgaaaagaaa acaaattctg 180
agactccaca atcaccaagc taaaggaaaa agtcaagctg ggaactgctt agggcaaagc 240
tgcctcccat tctattcaca gtcattcccc tgaggctcac ctgcatagct gattgcttcc 300
tttcccttat cgcttctgta aaaatgcaga ctactgagc cagactaaat tgtgtgttca 360
gtggaaggct gatcaagaac tcaaaagaat gcaacctttt gtctcttctc tactacaacc 420
aggaagcccc cacttaaggg ttgtcccacc ttactggact gaaccaaggc acatcttaca 480
cctactgatt gatgtctcat gtccccctaa g 511

```

```

<210> 234
<211> 221
<212> DNA
<213> Homo sapiens

```

```

<400> 234
caggtccagc gaaggggctt cataggtcac accaagcatg tccacataac cgaggaagct 60
ctctccatca gcatagcctc cgatgaccat ggtgttccac aaaggggtca tcttcgagcg 120
ccggctgtac atggccctgg tcagccatga atgaatagct ctaggactat agctgtgtcc 180
atctcccaga agctcctcat caatcaccat ctggccgaga c 221

```

```

<210> 235
<211> 381
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (33)
<223> n=A,T,C or G

```

```

<400> 235
ggtccaagaa agggacatct atgtgaaagt ganactgaga cagtgtctggc cacagggtcat 60
gctgcagaat aatacattcc caggcactgt cacgtggggg acccaagagg ccccaggagt 120
gacctataac ctctccagaa agaccactct gtgtggcatc acagtccaca cagttaaagg 180
aaatatattag acttaacaat cagacaccag ctcttactca cacttacact cacagcccac 240
acacaagtgt gcaaacatac acacacatat atatttcctg atacattcat ggaatatcag 300
agccctgccc tgaagtcgtt agtgtctctg ctccccaaac cgctgtctcc acattgggta 360
agctccctca agagacctca g 381

```

```

<210> 236
<211> 441
<212> DNA
<213> Homo sapiens

```

```

<400> 236
aggtcctggt gcccttttct tttgcccaac ttgcgcattt gggaattgga atatttacc 60
aacacctgta ctgcattgaa tatttgaagc aaataacttg gctttgatct tataggctca 120
cagatggagg aacgtacctt gaagttcaga tgagatttcg gacttttgag ttgatgtgta 180
aacagcttga gatttttggg gactactgag agatgataat tgtattgtgc aatatgagaa 240

```

65

```

ggacatgaga tttggtgggc atagggtgtga aatgacattg tttggatgtg tttaccctcc 300
aaatctcttg ttgaatgtga tcttaaacgt tgggtgggtgg cctagtggaa ggtgttgaat 360
catgggggtg gactcttcat aatttgctta gctccatccc cttggtgatg agcaagtcc 420
tgctctgttg tgtcacatga g                                     441

```

```

<210> 237
<211> 281
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(281)
<223> n=A,T,C or G

```

```

<400> 237
tcctaaaaaa ttagctgacc ttgttaaaaa tgttggcgtg agcagtatat tattacctat 60
ctttttttat tgtgtgtgtg ngtgtgtgtg ttaaaactaat tggctgaaat atctgcctgt 120
ttccctcttt acatttttct tgtttctttc cttattttatc tttgtccatc ttgagatcta 180
ctgtaaaagt aatnttttaa tgaaaaacann nccaagtnt actctcactg ggnttgggac 240
atcagatgta attgagaggc caacaggtaa gtcttcatgt c                                     281

```

```

<210> 238
<211> 141
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(141)
<223> n=A,T,C or G

```

```

<400> 238
gtctgcctcc tcctactgtt tccctctatn aaaaagcctc cttggcgag gttccctgag 60
ctgtgggatt ctgcactggg gcttnggatt ccctgatatg ttccttcaaa tccactgaga 120
attaaataaa catcgctaaa g                                     141

```

```

<210> 239
<211> 501
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(501)
<223> n=A,T,C or G

```

```

<400> 239
aacaatctaa acaaatccct cggttctann atacaatgga ttccccatat tggaaggact 60
ctgangcttt attccccac tatgcntatc ttatcathtt attattatac acacatccat 120
cctaaactat actaaagccc ttttcccatg catggatgga aatggaagat ttttttttaa 180
cttgttctag aagtcttaat atgggctgtt gccatgaagg cttgcagaat tgagtccatt 240
ttctagctgc ctttattcac atagtgatgg ggtactaaaa gtactgggtt gactcagaga 300
gtcgctgtca ttctgtcatt gctgctactc taacactgag caacactctc ccagtggcag 360
atcccctgta tcattccaag aggagcattc atccccttgc tctaatgatc aggaatgatg 420
cttattagaa aaçaaactgc ttgaccaggg aacaagtggc ttagcttaag naaacttggc 480
tttgctcana tccctgatcc t                                     501

```

```

<210> 240
<211> 451
<212> DNA
<213> Homo sapiens

```

```

<400> 240
tgctcctgaaa ggccattact aatagaaaaca cagcctttcc aatcctctgg aacatattct 60
gtctgggttt ttaatgtctg tggaaaaaaa ctaaacaagt ctctgtctca gttaagagaa 120
atctattggt ctgaagggtt ctgaacctct ttctggttct cagcagaagt aactgaagta 180
gatcaggaag gggctgcctc aggaaaattc ctatgcctca ggaattcagt gagaccctgg 240
gaaggaccag catgctaata agtgtcagt aatccacagt cttacttcc tgcctcataa 300
agggccaggt ctcccagta ccaagtcctt tcctcatgaa gttgtgttgc ctcaggctgt 360
ttagggacca ttgcctgtct tggtcacatg agtctgtctc cttactttag tccctgggca 420
atccttgctt aatgcttttg ttgactcaac g 451

```

```

<210> 241
<211> 411
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(411)
<223> n=A,T,C or G

```

```

<400> 241
aatctccagt gtgatggtat cggggttaga gcttcaatct ccagtgtgat ggtactgcag 60
cnagagcttc aatctocagt gngatggtat tagggttaga tcttcaatct ccagtgtgat 120
ggtatcaggg ttagagcttc agcctccagt gtgatggtat cagggttaga gcttcagcct 180
ccagtgtgat ggtatcgggg ttagatcttc aatccccagt ggtgggtggt agagcttcaa 240
tctccagtgt gatgggtatt ggggttagagc ttcaatctcc agtctgatgg tgtttcgga 300
tggggctttt aagatgtaat tagggtttaa gatcataagg gacctggtct gatggggatt 360
agtncgcttn tatgaagaga cacangaggg cttgctctat ctctgactct c 411

```

```

<210> 242
<211> 351
<212> DNA
<213> Homo sapiens

```

```

<400> 242
ttccccctca caacagtaga gacctacaca gtgaactttg gggacttctg agatcagcgt 60
cctaccaaga cccagccca actcaagcta cagcagcagc acttccaag cctgctgacc 120
acagtcacat caccatcag cacatggaag gccctggta tggacactga aaggaagggc 180
tggtcctgcc cctttgaggg ggtgcaaaca tgaactggac ctaagagcca gaggtgtgt 240
agaggctcct gctccacctg ccagtctcgt aagaaatggg gttgctgcag tggtggagta 300
ggggcagagg gagggagcca aggtcactcc aataaaacaa gctcatggca c 351

```

```

<210> 243
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<400> 243
gtctgtgctt tatcaggaaa agcacaagaa tatgtttttc tacctaaaac cctcttctac 60
tttaaaaatg gtttgctgaa tttttctatg tttttaaaat gtttttatgc ttttttttaa 120
acacgtaaag gatggaacct aatcctctcc cgagacgcct cctttgtgtt aatgcctatt 180
cttacaacag agaaacaagt acattaatat aaaaacgagt tgattattgg ggtataaaa 240
a 241

```

```

<210> 244
<211> 301
<212> DNA
<213> Homo sapiens

```

```

<400> 244
ggtccagagc aatagcgtct gtgggtgaagc gcctgcactc ctcgggagac atgcctggct 60

```

67

```
tatatgctgc atccacataa ccatagataa aggtgctgcc ggagccacca atggcaaaag 120
gctgtcgagt cagcattcct cccagggttc catatacctg acctccttca cgttggtccc 180
agccagctac catgagatgt gcagacaagt cctctcgata tttatagctg atatttctca 240
ccacatttgc agcagccaaa acaagtggag gttcctccag ttctatccca tggagctcca 300
g                                                                 301
```

<210> 245
 <211> 391
 <212> DNA
 <213> Homo sapiens

```
<400> 245
ctgacactgc tgatgtgggc cggggggcgc cgaggcacia ctggtggccg gaccattgag 60
gcacctggag ggtaggcagc ttgtgggtgca gacaccacag agagagaaaa gttggatgga 120
gtggtgggaa taatcagggt ggcacactgt gcctagaagc ttccagggcc accaagagaa 180
tggaaggga aactacaaca ttcacaacag aaataggagt caattcactt agaccagaa 240
ctccagaaag ggggagtgtg ggaatctaca atttcaaagc cagctcgtgt ctacctagag 300
cccaaactg cataagcacc aggattgtac acctagtcc ctcaagatag tttcaagtga 360
gcgtgcaatt cactcttaca gaggagggcc t                                                                 391
```

<210> 246
 <211> 291
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(291)
 <223> n=A,T,C or G

```
<400> 246
tcctccacag gggaagcagg aagttingacc agcttcaggc tggaacgtgc ccagggcaca 60
gagctggcaa ggtgc aaagn cntctgcaga atattcacca gtttgacaca gacctccaca 120
ttcagacata ttccaagctt ctgggggtctt cagggcccca gaatttcctg gtcttgggca 180
tggtncacaa gtcattttgtc ctctctcatt ttggaagggt ccatttggac ataaaatgca 240
agcgttctcg tgctncatna taataggctc cagcctgcac tgacacattt g                                                                 291
```

<210> 247
 <211> 471
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(471)
 <223> n=A,T,C or G

```
<400> 247
cactgagtga atgagtatat aatttatgaa aacagaaaag tgctttggaa aaaaaaaaaag 60
acaacaggag tacatacagn gaaccaaaaa gagtgtacca ggaggagcan accctgaaca 120
gttanaacta tggaatcgc tatgctttgt gttgtcacag gaggtaaaat aggaataccc 180
tgcatacaat aaatatatat tggataaata actaagcctg ataccctttt caatgcgtta 240
tacanactnt atcatcacac cactaatcta agttctcana agttaaacat tacaagactt 300
cagaacaaca taggcgtnnt tggctccatt taacanaana aggaccatag tgatcattta 360
atctctatga gtctgtctta tcttctggaa aaggggccta acaccatttc cttttgcaaa 420
aaggtagctg ccttgcttcc agttctacca tcctntagca acccatcttt n                                                                 471
```

<210> 248
 <211> 551
 <212> DNA
 <213> Homo sapiens

<400> 248
ccatgggatc aggaatgggg tcaggtcagt tgacctgagc ataccatta aacatgttca 60
aatgtcccca tcccaccac tcacatgaca tggctccga gccctgagat ctgtatccca 120
agaacctcag ttgagaaata tttatggcag cttcactgtt gctcaagagc ctgggtattg 180
tagcagcctg ggggcagggt gtccctaagt ttctccaagt tcttcacatc agccagaatc 240
ccatctatgc ttgtctccag caaatggagg tggccctct gctgacgtgc cctctcttcc 300
agctctgaca tcatgggccg cagttggctg ttgatctggg tcttggctcg ggaaagcttc 360
tgctccagta agaccagccc ctcttcatct aactgagag gctgggtccat cagatgcagg 420
aggcgtcta atgtgttgag tgtgtcttgg attgtaacct cagcgttctt ggctctggta 480
tcaaccttct gggcttctgt aatcaccatc tgtactgcat ccatattcgt gtcgaactcc 540
agctccttcc t 551

<210> 249
<211> 181
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(181)
<223> n=A,T,C or G

<400> 249
atntccagag ggaccgtaag actggtacaa gtttacacca taagaggcga cgtggtcagc 60
cacaatgtct tcacctccac agggggtcat caccgnggtc agggcaaggg ccccagcat 120
cagagctttg tttaggatca tcctcttccc aaggcagcct tagcagttgc tgacctgcc 180
g 181

<210> 250
<211> 551
<212> DNA
<213> Homo sapiens

<400> 250
tctgtagcta ggatgagctg gctctcaagc aaaagtttgt cttcctgggt ccatttgttg 60
ttatcacttg ttattgaatg tacatcaca attaaagtct gcattgttgg acgtaagaga 120
atgtgccgac tttggttaacc aggagatttc atgttactgg actgcctgta gtcacgtatt 180
tctgctatga cacatccgca atgaaaaata ttaacctgag atttttctag gagatcaacc 240
aaaataggag gtaattcttc tgcattccaa tattcaagca actctccttc ttcatagggc 300
agtcgaatgg tctcggaatc tgatccgttt ttccctctga gcatcagaga atatccctca 360
tttctctggg atagattgac cactaaacat gacaaagtct cttgcataac aagcttctct 420
aacaagttca catttcttct taatttctta acttcagggt ctttttcaca ttcttcaata 480
tacaagtcac aaagtttttg aaatacagat tttcttccac ttgataggta tttcctttta 540
ggaggctctc g 551

<210> 251
<211> 441
<212> DNA
<213> Homo sapiens

<400> 251
tgtctgctct cccatcctgg ttactatgag tcgctcttgg cagaaaggac cacagatgga 60
gagcttggca ctcgctccaa ctttgccgaa aaggaggaca ccaccaagt agtaggtaaa 120
aacacaattt tagcagcagt gaaataaaaa gaggaagtga ggatggggcc aggccgcaac 180
tataattaaa ctgtctgttt aggagaagct gaatccagaa gaaacacaag ctgtaaagt 240
agagaggaca gggagcagg ctttggaga gcaggagagg acaggctgtc accaagcgct 300
gctcggactc tgccctgaaa gatttgaatt ggacactgtc cagtcacgtg tgtggcaaac 360
cgtactccaa gcacttttct cacggcagag gaaggagctg ccatggctgt acccctgaac 420
gtttgtgggg ccagcgatgt g 441

<210> 252
<211> 406

<212> DNA

<213> Homo sapiens

<400> 252

```

tttttttttg aacaagtaaa aattttcttta tttgctgaca ataagataac ctacagggaa 60
aacctgatga aatctatttaa aaagttacta aaactaataa aagaatttag gaaggttata 120
gaatgtaaga ccaagacaca aaaatcaatt acatttctat ataatagcaa tgaacagata 180
ctgaaatttt aaaaactaaa tcatttttaca aaagtatcac aatatgaaac actccgggat 240
aaattggata aaagatgtgc aagactgtac aaaagctaca aaacatttat gaaggaaatt 300
ggaagataga aacaagatag aaaatgaaaa tattgtcaag agtttcagat agaaaatgaa 360
aacaagcta agacaagtat tggagaagta tagaagatag aaaaaa 406

```

<210> 253

<211> 544

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (224)

<223> n=A,T,C or G

<400> 253

```

gaaggagtgc agtagcaaag tcacacctgt ccaattccct gagctttgct cactcagcta 60
atgggatggc aaaggtggtg gtgctttcat cttcaggcag aagcctctgc ccatccccct 120
caagggctgc agggccagtt ctcatgtctg ccttgggtgg gcactctgta acagaggaga 180
acgtctgggt ggcggcagca gctttgctct gactgcctac aaanctaag cttggtgcta 240
gaaacatcat cattattaaa cttcagaaaa gcagcagcca tgttcagtca ggctcatgct 300
gcctcactgc ttaagtgcct gcaggagccg cctgccaaag tccccctcct acacctggca 360
cactggggtc tgcacaaggc tttgtcaacc aaagacagct tccccctttt gattgcctgt 420
agacttttga gccaaagaaac actctgtgtg actctacaca cacttcaggt ggtttgtgct 480
tcaaagtcac tgatgcaact tgaaaggaaa cagtttaatg gtggaaatga actaccattt 544
ataa

```

<210> 254

<211> 339

<212> DNA

<213> Homo sapiens

<400> 254

```

tggcattcag ggcagtgtct tctgcatctc ctaggaacct cgggagcggc agctccggcg 60
cctggttagc agaggcgggt tccggagatc cgggcctcac ttctgccac tgtggttagg 120
ggtgagtcct gcaaagtgtt agtgatttgc tcaaggtgcc catttcgcag gaattggagc 180
ccaggccagt tctctgagcc tatcattagg gctaaaggag tgcgtgatca gaatggtgtc 240
tggacgggtc tacttgtcct gcctgctgct ggggtccctg ggctctatgt gcactcctct 300
cactatctac tggatgcagt actggcgttg tggctttgc

```

<210> 255

<211> 405

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(405)

<223> n=A,T,C or G

<400> 255

```

gagggttttt nttttttttt tttttttttt caattaaana tttgatttat tcaagtatgt 60
gaaaacattn tacaatggaa acttttntta aatgtgcgat gtntctgtgt atggaccacn 120
cacatacagc catgctgttt caaaaaactt gaaatgccat tgatagttaa aaaactntac 180
ncccgatgga aaatcgagga aaacaattta atgtttcatn tgaatccana ggngcatcaa 240

```

```

attaaatgac agctccactt ggcaaataat agctgttact tgatggtatc caaaaaaaaa 300
tggttgggga tggataaatt caaaaatgct tccccaaagg ngggnggttt ttaaaaagtt 360
tcaggnccaca acccttgcan aaaacactga tgcccaacac antga 405

```

```

<210> 256
<211> 209
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (6)
<223> n=A,T,C or G

```

```

<400> 256
gggcangtct ggtcctctcc ccacatgtca cactctctcc agcctctccc ccaaccctgc 60
tctccctcct cccctgccct agcccaggga cagagtctag gaggagcctg gggcagagct 120
ggaggcagga agagagcact ggacagacag ctatggtttg gattggggaa gaggttagga 180
agtaggttct taaagaccct ttttagta 209

```

```

<210> 257
<211> 343
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(343)
<223> n=A,T,C or G

```

```

<400> 257
tctggacacc ataatccctt ttaagtggct ggatgggtcac acctctccca ttgacaagct 60
gggttaagtc aatagggttg ctaggatcaa cagaccccaa atcaataaga tactgcagtc 120
tattgagact caaaggctta tactggcgtc tgaaactatg tccttcgtta aacccgatt 180
ttgggattcg gatgtaaaat ggagtctggc ctccctcaaa gcccaagcgg ggccgggttc 240
ctctttgcct ttctccttta tggcctctgc cacatcttct acctcttctc cgacctcttg 300
gtcttntctc nggtttcttg gagccgggat tcggctttaa gtn 343

```

```

<210> 258
<211> 519
<212> DNA
<213> Homo sapiens

```

```

<400> 258
gcggcttctg acttctagaa gactaaggct ggtctgtggt tgcttggttg cccacctttg 60
gctgataccc agagaacctg ggcacttgct gcctgatgcc caccctgcc agtcattcct 120
ccattcaccg agcgggaggt gggatgtgag acagcccaca ttggaaaatc cagaaaaccg 180
ggaacagggg tttgcccttc acaattctac tcccagatc ctctccctg gacacaggag 240
accacagggg caggacccta agatctgggg aaaggaggtc ctgagaacct tgaggtacct 300
ttagatcctt ttctaccac tttcctatgg aggattccaa gtcaccactt ctctcaccg 360
cttctaccag ggtccaggac taaggcgttt tctccatagc ctcaacattt tgggaatctt 420
cccttaatca cccttgctcc tctgggtgc ctggaagatg gactggcaga gacctctttg 480
ttgcgttttg tgctttgatg ccaggaatgc cgctagtt 519

```

```

<210> 259
<211> 371
<212> DNA
<213> Homo sapiens

```

```

<400> 259
attgtcaact atatacacag tagtgaggaa taaaatgcac acaaaacaat ggatagaata 60
tgaaaatgtc ttctaaatat gaccagtcta gcatagaacc ttcttctctt ctttctcagg 120

```

```

tcttccagct ccatgtcatc taaccactt aacaaacgtg gacgtatcgc ttccagaggc 180
cgtcttaaca actccatttc caaaagtcac ctccagaaga catgtatttt ctatgatttc 240
ttttaaacia atgagaattt acaagatgtg taactttcta actctatttt atcatatcgtc 300
ggcaacctct ttccatctag aagggctaga tgtgacaaat gttttctatt aaaagggttg 360
ggtggagttg a 371

```

```

<210> 260
<211> 430
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(430)
<223> n=A,T,C or G

```

```

<400> 260
ttggattttt tgacttgoga tttcagtttt tttacttttt tttttttttt ttttganaaa 60
tactatatatt attgtcaaag agtggtacat aggtgagttg tcatcttccc tctcatgccg 120
gtatactctg cttcgctgtt tcagtaaaag ttttccgtag ttctgaacgt cccttgacca 180
caccataana caagcgcaag tcaactcanaa ttgccactgg aaaactggct caactatcat 240
ttgaggaaaag actganaaaag cctatcccaa agtaatggac atgcaccaac atcgcggtac 300
ctacatgttc ccgtttttct gccaatctac ctgtgtttcc aagataaatt accaccagg 360
gagtcacttc ctgctatgtg aacaaaaacc cggtttcttt ctggagggtgc ttgactactc 420
tctcgnagac 430

```

```

<210> 261
<211> 365
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (178)
<223> n=A,T,C or G

```

```

<400> 261
tcttgacgat agccatggct gtaccactta actatgattc tattccaact gtccagaatc 60
atatcacaaa atgacttgta cacagtagtt tacaacgact cccaagagag gaaaaaaaaa 120
aaaaaaagacg cctcaaaatt cactcaactt ttgagacagc aatggcaata ggcagcanag 180
aagctatgct gcaactgagg gcacatatca ttgaagatgt cacaggagtt taagagacag 240
gctggaaaaa atctcatact aagcaaacag tagtatctca taccaagcaa aaccaagtag 300
tatctgctca gcctgccgct aacagatctc acaatcacca actgtgcttt aggactgtca 360
ccaaa 365

```

```

<210> 262
<211> 500
<212> DNA
<213> Homo sapiens

```

```

<400> 262
cctagatgtc atttgggacc cttcacaacc attttgaagc cctgtttgag tccctgggat 60
atgtgagctg tttctatgca taatggatat tcgggggttaa caacagtccc ctgcttggct 120
tctattctga atccttttct ttcaccatgg ggtgcctgaa ggggtggctga tgcatagggt 180
acaatggcac ccagtgtaaa gcagctacaa ttaggagttg atgtgttctg tagcatccta 240
tttaaataag cctattttat cctttggccc gtcaactctg ttatctgctg cttgtactgg 300
tgctgtact tttctgactc tcattgacca tattccacga ccatggttgt catccattac 360
ttgatcctac tttacatgtc tagtctgtgt ggttggtggg gaataggctt ctttttacat 420
ggtgctgcca gccagctaa ttaatggtgc acgtggactt ttagcaagcg ggctcactgg 480
aagagactga acctggcatg 500

```

```

<210> 263

```


<211> 413
<212> DNA
<213> Homo sapiens

<400> 263
ctcagagagg ttgaaagatt tgcctacgaa agggacagtg atgaagctaa gctctagatc 60
caggatgtct gacttcaaatt tgaaactccc aaagtaatga gtttggaagg gtggggtgtg 120
gcctttccag gatgggggtc ttttctgctc ccagcggata gtgaaacccc tgtctgcacc 180
tggttgggcg tgttgctttc ccaaaggttt ttttttttagg tccgtcgtctg tcttgtggat 240
taggcattat tatctttact ttgtctccaa ataacctgga gaatggagag agtagtgacc 300
agctcagggc cacagtgcga tgaggaccat cttctcacct ctctaaatgc aggaagaaac 360
gcagagtaac gtggaagtgg tccacaccta ccgccagcac attgtgaatg aca 413

<210> 264
<211> 524
<212> DNA
<213> Homo sapiens

<400> 264
tccaatgggg ccctgagagc tgtgacagga actcacactc tggcactggc agcaaaacac 60
cattccaccc cactcatcgt ctgtgcacct atgttcaaac tttctccaca gttccccaat 120
gaagaagact catttcataa gtttgtggct cctgaagaag tcctgccatt cacagaaggg 180
gacattcttg agaaggtcag cgtgcattgc cctgtgtttg actacgttcc cccagagctc 240
attacctctt ttatctccaa cattgggtggg aatgcacctt cctacatcta ccgctgatg 300
agtgaactct accatcctga tgatcatgtt ttatgaccga ccacacgtgt cctaagcaga 360
ttgcttaggc agatacagaa tgaagaggag acttgagtgt tgctgctgaa gcacatcctt 420
gcaatgtggg agtgcacagg agtccaccta aaaaaaaaaa tccttgatac tgttgccctgc 480
ctttttagtc accccgtaac aagggcacac atccaggact gtgt 524

<210> 265
<211> 344
<212> DNA
<213> Homo sapiens

<400> 265
tcctttcttc tacttcagga gatgattcaa agttacttgt ggacattttot ttaagttctg 60
aagacaaatg agacaggatt tggcctgcgg gttcttcaga cttctctacc acctccatta 120
actcttcatc ttggccttgac gtaggcaatg cactattttg ctcttttggt tctggagatg 180
accagcacc acttctttct cttggcgggg ttctaagtgt gtctttgaat accagtgaag 240
actcaggcct atcctgtact ggaaaggac taaatttgtc tttctgtcta ggaggatgat 300
cagtagcatc ctctgaggg ggtaaggcca tttctctttt ttga 344

<210> 266
<211> 210
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (78)
<223> n=A,T,C or G

<400> 266
ccacaatgtc cataacttga gcaggctttg gcatcccacc acccccttca gaccaatata 60
cactatgttg gaggaacnac tttaaaatgt aaaatgagaa atgggcactg aacactccat 120
cctcactccc aacagcccac ccacacacct cttcaactgc tatccaaaca tggaggagct 180
cttgtggaag agaggctcaa caccaataa 210

<210> 267
<211> 238
<212> DNA
<213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(238)
 <223> n=A,T,C or G

<400> 267
 tcggnccctcc caccctctna ctgaaattct ntgaaattct cccctttggg atgaggatgg 60
 caaccccagc catgtaccct cccaacctgg gacccgacct aataccctaa catcctgctg 120
 acagtggctg ttctcgctgg gcaggcgctc caaagcacat cgagccagat tcaggcagag 180
 tggaaactggc ccctcagcca tcagtggagg tggcctggga ggctctaccc tgaacggg 238

<210> 268
 <211> 461
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (459)
 <223> n=A,T,C or G

<400> 268
 tcctcaagga catgcccctt gatagaaact cagttcctgt ctccagttcc ctccctggacc 60
 tgatccccca aatgcagggc ctgggactat atccagttcc ttattttcag agggcccatgc 120
 acaagatgca cagcaaataa gtgctgaata aagaccagc tactgctagc ttaccctgct 180
 ccaaacattc accaagtcct cagcaaagag ggccatccat tcacctcttc taaaaacaca 240
 ctgagctccc cagtctatcc cccaagatat gcttggctcc caactatccc tcctctctca 300
 ttccaagcc agtttccctt ttctaagtat actgatatta ccaaagacac tgacaatctt 360
 cttttcctac ctctcccag tgactagggt tgcagcagga gctctataag tcctagtata 420
 cagcagaagc tccataaatg tgtgctgacc taacattang c 461

<210> 269
 <211> 434
 <212> DNA
 <213> Homo sapiens

<400> 269
 ctgtgttggt gagcaccgat tcccactcaa tatggcgtgg cttacagtct tcattaggtt 60
 cccgctccca accagaatga ggaatgatca cttcatctgt caaggcatgc agtgcattgt 120
 ccacaatctc cattttgatt gagtcatggg atgaaagatt ccacagggtt ccggtataaa 180
 cttcagtaag gtccatatca cgagcctttc gaagcaatcg cacaagggca ggcacaccat 240
 cacagttttt tatggcaatc ttgttatcct ggtcacgtcc aaaagagata ttcttgagag 300
 ctccacaggc tccaagggtc acttcctttt tgggatggtc taacaatccc accagtactg 360
 ggatgccctt gagcttccgc acgtcagtct tcacctgtgc attgcggtag cataagtgtt 420
 gcaggatatg aaga 434

<210> 270
 <211> 156
 <212> DNA
 <213> Homo sapiens

<400> 270
 ctgcaccagc gattaccagt ggcattcaaa tactgtgtga ctaaggattt tgtatgctcc 60
 ccagtagaac cagaatcaga caggtatgag ctagtcaaca gcaagtcttt gttggattcg 120
 agtaggctca ggatctgctg aaggtcggag gaggta 156

<210> 271
 <211> 533
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(533)
 <223> n=A,T,C or G

<400> 271
 ccactgtcac ggtctgtctg acacttactg ccaaacgcat ggcaaggaaa aactgcttag 60
 tgaagaactt agaagctgtg gagaccttgg ggtccacgtn caccatctgc tctgataaaa 120
 ctggaactct gactcanaac cggatgacag tggcccacat gtggtttgac aatcaaattcc 180
 atgaagctga tacgacagag aatcagagtg gtgtctcttt tgacaagact tcagctacct 240
 ggcttgctct gtccagaatt gcaggtcttt gtaacagggc agtgtttcag gctaaccagg 300
 aaaacctacc tattcttaag cgggcagttg caggagatgc ctctgagtca gcactcttaa 360
 agtgcataga gctgtgctgt ggntncgtga aggagatgag agaaagatac nccaaaatcg 420
 tcgagatacc cttcaactcc accaacaagt accagttgtc tattcataag aacccaaca 480
 catcgagacc ccaacacctg ttggtgatga agggcgcccc agaaaggatc cta 533

<210> 272
 <211> 630
 <212> DNA
 <213> Homo sapiens

<400> 272
 tgggtattttt ctttttcttt tggatgtttt atactttttt ttcttttttc ttctctattc 60
 ttttcttcgc cttcccgtag ttctgtcttc cagttttcca cttcaaactt ctatcttctc 120
 caaattgttt catctacca ctccaatta atctttccat ttctgtctgc gtttagtaaa 180
 tgcgttaact aggccttaaa tgacgcaatt ctccctgcgt catggatttc aaggctcttt 240
 aatcaccttc ggtttaatct ctttttaaaa gatcgcttc aaattatttt aatcacctac 300
 aactttttaa ctaaacctta agctgtttta gtcaccttca ttttaattcta aaagcattgc 360
 ccttctattg gtattaattc ggggctctgt agtcctttct ctcaattttc ttttaaatat 420
 attttttact ccatgaagaa gcttcatctc aacctccgtc atgtttttaga aaccttttat 480
 cttttccttc ctcatgctac tcttctaagt cttcatattt tctcttaaaa tcttaagcta 540
 ttaaaattac gttaaaaact taacgctaag caatatctta gtaacctatt gactatattt 600
 tttaagtagt tgtattaatc tctatctttc 630

<210> 273
 <211> 400
 <212> DNA
 <213> Homo sapiens

<400> 273
 tctggtttgc cctccagttc attctgaatc tagacttgct cagcctaatc aagttcctgt 60
 acaaccagaa gcgacacagg ttccttttgg atcatocaca agtgaggggt acacagcatc 120
 tcaacccttg taccagcctt ctcatgctac agagcaacga ccacagaagg aaccaattga 180
 tcagattcag gcaacaatct ctttaaatat agaccagact acagcatcat catcccttcc 240
 tgctgcgtct cagcctcaag tatttcaggc tgggacaagc aaacctttac atagcagtg 300
 aatcaatgta aatgcagctc cattccaatc catgcaaagc gtgttcaata tgaatgcccc 360
 agttcctcct gttaatgaac cagaaacttt aaaacagcaa 400

<210> 274
 <211> 351
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (2)
 <223> n=A,T,C or G

<400> 274
 tntgagtatg tcccagagaa ggtgaagaaa gcggaaaaga aattagaaga gaatccatat 60
 gaccttgatg cttggagcat tctcattcga gaggcacaga atcaacctat agacaaagca 120
 cggaagactt atgaacgcct tgttgcccag ttccccagtt ctggcagatt ctggaaactg 180

75

```

tacattgaag cagaggttac tattttattt tattttttct tatatcagta ttgcagcatt 240
cactgtagt atagaaaaca agttaggaac atagccaatt aggacaagga ggattttaat 300
gtgtcttacc tttattttgt aaaataggta taaaggagta attaaaaatga a 351

```

```

<210> 275
<211> 381
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(381)
<223> n=A,T,C or G

```

```

<400> 275
gcgnggtcgc nnncgaggtc tgagaagccc ataccactat ttgttgagaa atgtgtggaa 60
tttattgaag atacagggtt atgtaccgaa ggactctacc gtgtcagcgg gaataaaaact 120
gaccaagaca atattcaaaa gcagtttgat caagatcata atatcaatct agtgtcaatg 180
gaagtaacag taaatgctgt agctggagcc cttaaagctt tctttgcaga tctgccagat 240
cctttaattc catattctct tcatccagaa ctattggaag cagcaaaaat cccggataaa 300
acagaacgtc ttcatgcctt gaaagaaatt gttaagaaat ttcatcctgt aaactatgat 360
gtattcagat acgtgataac a 381

```

```

<210> 276
<211> 390
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (5)
<223> n=A,T,C or G

```

```

<400> 276
gctcngactc cggcgaggacc tgctcggagg aatggcgccg cggggttcaa gcaactgtctt 60
cctgtttggcc ctgacaatca tagccagcac ctgggctctg acgcccactc actacctcac 120
caagcatgac gtggagagac taaaagcctc gctggatcgc cctttcacia atttggaatc 180
tgccttctac tccatcgtgg gactcagcag ccttggtgct caggtgccag atgcaaaaga 240
agcatgtacc tacatcagat ctaaccttga tcccagcaat gtggattccc tcttctacgc 300
tgcccaggcc agccaggccc tctcaggatg tgagatctct atttcaaatg agaccaaaaga 360
tctgcttctg gcagacctcg gccgcgacca 390

```

```

<210> 277
<211> 378
<212> DNA
<213> Homo sapiens

```

```

<400> 277
tgggaacttc tggggtagga cgttgtctgc tatctccagt tccacagacc caaccagtta 60
cgatggtttt ggaccattta tgccgggatt cgacatcatt ccctataatg atctgcccg 120
actggagcgt gctcttcagg atccaaatgt ggctgcgttc atggtagaac caattcagg 180
tgaagcaggc gttgtttgtc cggatccagg ttacctaatg ggagtgcgag agctctgcac 240
caggcaccag gttctcttta ttgctgatga aatacagaca ggattggcca gaactggtag 300
atggctggct gttgattatg aaaatgtcag acctgatata gtcctccttg gaaaggccct 360
ttctgggggc ttataccc 378

```

```

<210> 278
<211> 366
<212> DNA
<213> Homo sapiens

```

```

<400> 278

```

76

```

ggagggcaca ttccttttca cctcagagtc ggtcggggaa ggccaccag ataagatttg 60
tgaccaaaacc agtgatgctg tccttgatgc ccaccticag caggatcctg atgccaaagt 120
agcttgtgaa actgttgcta aaactggaat gatccttctt gctggggaaa ttacatccag 180
agctgctgtt gactaccaga aagtgggtcg tgaagctgtt aaacacattg gatatgatga 240
ttcttccaaa ggttttgact acaagacttg taacgtgctg gtagccttgg agcaacagtc 300
accagatatt gctcaagggtg ttcattctga cagaaatgaa gaagacattg gtgctggaga 360
ccaggg                                           366

```

<210> 279

<211> 435

<212> DNA

<213> Homo sapiens

<400> 279

```

cctaagaact gagacttgtg acacaaggcc aacgacctaa gattagccca gggttgtagc 60
tggaagacct acaacccaag gatggaaggc cctgtgcaca aagcctacct agatggatag 120
aggacccaag cgaaaaagat atctcaagac taacggccgg aatctggagg cccatgaccc 180
agaacccagg aaggatagaa gcttgaagac ctggggaaat cccaagatga gaaccctaaa 240
ccctacctct ttctatttgt ttacacttct tactcttaga tatttccagt tctcctgttt 300
atcttttaagc ctgattcttt tgagatgtac tttttgatgt tgccgggttac ctttagattg 360
acaagtatta tgcttgacca gtcttgagcc agctttaaat cacagctttt acctatttgt 420
taggctatag tgttt                                           435

```

<210> 280

<211> 435

<212> DNA

<213> Homo sapiens

<400> 280

```

tctggatgag ctgctaactg agcacaggat gacctgggac ccagcccagc caccocgaga 60
cctgactgag gccttcctgg caaagaagga gaaggccaag gggagccctg agagcagctt 120
caatgatgag aacctgcgca tagtggtggg taacctgttc cttgccggga tggtagaccac 180
ctcgaccacg ctggcctggg gcctcctgct catgatccta cacctggatg tgcagcgtga 240
gccagacct gtccgggcgg ccgctcgaaa ttccagcaca ctggcgcccg ttactagtgg 300
atccgagctc ggtaccaagc ttggcgtaat catggtcata gctgtttcct gtgtgaaatt 360
gttatccgct cacaattcca cacaacatac gagccggaag cataaagtgt aaagcctggg 420
gtgcctaaty agtga                                           435

```

<210> 281

<211> 440

<212> DNA

<213> Homo sapiens

<400> 281

```

catctgatct ataaatgcgg tggcatcgac aaaagaacca ttgaaaaatt tgagaaggag 60
gctgctgaga tgggaaaggg ctccctcaag tatgcctggg tcttgataa actgaaagct 120
gagcgtgaac gtggtatcac cattgatata tccttggtga aatttgagac cagcaagtac 180
tatgtgacta tcattgatgc ccaggacac agagacttta tcaaaaacat gattacaggg 240
acatctcagg ctgactgtgc tgtcctgatt gttgctgctg gtgttggtga atttgaagct 300
ggtatctcca agaattgggca gacccgagag catgcccttc tggcttacac actgggtgtg 360
aaacaactaa ttgtcggtgt taacaaaatg gattccactg agccccctac agccagaaga 420
gatatgagga aattgttaag                                           440

```

<210> 282

<211> 502

<212> DNA

<213> Homo sapiens

<400> 282

```

tctgtggcgc aggagccccc tccccggcca gctctgacgt ctccaccgca gggactgggtg 60
cttctcggag ctccactccg tcagactccg gtggaagtga cgtggacctg gatccactg 120
atggcaagct cttcccagc gatggttttc gtgactgcaa gaagggggat cccaagcacg 180

```

77

```

ggaagcggaa acgaggccgg ccccgaaagc tgagcaaaga gtactgggac tgtctcgagg 240
gcaagaagag caagcacgcg cccagaggca cccacctgtg ggagttcatc cgggacatcc 300
tcatccaccc ggagctcaac gagggcctca tgaagtggga gaatcggcat gaaggcgtct 360
tcaagttcct gcgctccgag gctgtggccc aactatgggg ccaaaagaaa aagaacagca 420
acatgacctg cgagaagctg agccggggcca tgaggtacta ctacaaacgg gagatcctgg 480
aacgggtgga tggccggcga ct                                     502

```

```

<210> 283
<211> 433
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(433)
<223> n=A,T,C or G

```

```

<400> 283
ccatattaga ttactggaac atctaagcat cagtgtgtga ccatgcgaac aaaagacttc 60
ggggagtgtc tattttttaa aaggtttatg tgtgtcgagg cagttgtaaa agatttactg 120
cagaatcaan cccactttta ggcttangac caggttctaa ctatctaaaa atattgactg 180
ataacaaaaa gtgttctaaa tgtggctatt ctgatccata nttgnttttt aaagaaaaaa 240
antgtntata cagaaagagt ntaaaagtgc tgtgaattna atgcaaatta gncnccantc 300
ttgacttccc aaanacttga ttnatacctt tnaactcctn cnnttcctgn ncttcnttaa 360
mntcaatnat tnggnagtnn anggcctnct gnanaacacc nttncnctgn ccncgcaatc 420
canccgcctt nan                                     433

```

```

<210> 284
<211> 479
<212> DNA
<213> Homo sapiens

```

```

<400> 284
tctggaagga tcagggatct gagcaaagcc aagtttactt aagctaagcc acttgttcct 60
gggtcaagca gtttgttttc taataagcat cattcctgat cattagagca aagggatgaa 120
tgctcctctt ggaatgatac aggggatctg ccactgggag agtggtgctc agtggttagag 180
tagcagcaat gacagaatga cagcgactct ctgagtcaac ccagtacttt tagtaccocg 240
tcactatgtg aataaaggca gctagaaaat ggactcaatt ctgcaagcct tcatggcaac 300
agcccatatt aagacttcta gaacaagtta aaaaaaaatc ttccatttcc atccatgcat 360
gggaaaaggg ctttagtata gtttaggatg gatgtgtgta taataataaa atgataagat 420
atgcatagtg ggggaataaa gcctcagagt ccttcagta tggggaatcc attgtatct 479

```

```

<210> 285
<211> 435
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(435)
<223> n=A,T,C or G

```

```

<400> 285
tttttttttt tttttttttt tcaatanaaa tgccataatt tattccattg tataaaaaag 60
tcatccttat gtaacaaaat gtnttcttan aanaanaaat atattatttc aggtcataaa 120
taatcagcaa acatacaact gttggcaact aaaaaaaaac ccaacactgg tattttccat 180
cagngctgaa aacaaacctg cttaaanata tttttacagg gatagtnacg tinctaaaaa 240
caaaaattga ggtatttttg ttcttctagg agtagacaat gacatttttg gangggcaga 300
cccctnnccc aaaaaataaa ataagggnat nttcttcant atngaannnn ggggggcccc 360
cggggaaaaa naaaccttgg gnnnggggtt tggcccaagc ccttgaaaaa aaantttntt 420
tcccaaaaaa aacng                                     435

```

<210> 286
<211> 301
<212> DNA
<213> Homo sapiens

<400> 286
cctggtttct ggtggcctct atgaatccca ttaggggtgc agaccgtact ccatccctcc 60
ctgtgagcac cacgtcaacg gctcccgcc cccatgcacg ggggagggag ataccccca 120
gtgtagcaag atctgtgagc ctggctacag cccgacctac aaacaggaca agcactacgg 180
atacaattcc tacagcgtct ccaatagcga gaaggacatc atggccgaga tctacaaaaa 240
cggccccgtg gagggagctt tctctgtgta ttcggacttc ctgctctaca agtcaggagt 300
g 301

<210> 287
<211> 432
<212> DNA
<213> Homo sapiens

<400> 287
tccagcttgt tgccagcatg agaaccgcca ttgatgacat tgaacgccgg gactggcagg 60
atgacttcag agttgccagc caagtcagcg atgtggcggg acaggggggac ccccttctca 120
acggcaccag ctttgacagc ggcaaggagc acccccagaa tggcggttcgc accaaactta 180
gatttatatt ctgttccatc catctcgatc atcagtttgt caatcttctc ttgttctgtg 240
acgttcagtt tcttgctaac cagggcaggc gcaatagttt tattgatgtg ctcaacagcc 300
tttgagacac ctttcccat atagcgagtc ttatcattgt cccggagctc tagggcctca 360
tagataccag ttgaagcacc actgggcaca gcagctctga agagacctt tgagggtgaag 420
agatcaacct ca 432

<210> 288
<211> 326
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (254)
<223> n=A,T,C or G

<400> 288
tctggctcaa gtcaaagtcc tggctcctct ctccgcctcc ttcttcatca tagtaataaa 60
cgttgtcccg ggtgtcatcc tctgggggca gtaagggctc tttgaccacc gctctcctcc 120
gaagaacacg caagagcagc agaatcagaa ttagcaaaagc aagaattcct ccaagaatcc 180
ccagaatggc aggaatttgc aatcctgctt cgacaggctg tgccttccta cagacgcccg 240
cggccccctc acantcacac acgtgacct ctaagggtgg cacttgggtt ttattctggg 300
tatccatgag cttgagattg attttg 326

<210> 289
<211> 451
<212> DNA
<213> Homo sapiens

<400> 289
gtccccgtgt ggctgtgccg ttggctcctgt gcggtcactt agccaagatg cctgaggaaa 60
cccagacca agaccaaccg atggaggagg aggaggttga gacgttcgcc tttcaggcag 120
aaattgccca gttgatgtca ttgatcatca atactttcta ctgcaacaaa gagatctttc 180
tgagagagct catttcaaatt tcatcagatg cattggacaa aatccggtat gaaagcttga 240
cagatcccg taaattagac tctgggaaag agctgcata taaccttata ccgaacaaac 300
aagatcgaac tctcactatt gtggatactg gaattggaat gaccaaggct gacttgatca 360
ataaccttgg tactatcgcc aagtctggga ccaaagcggt catggaagct ttgcaggctg 420
gtgcagatat ctctatgatt ggacctcggc c 451

<210> 290

<211> 494
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (421)
 <223> n=A,T,C or G

<400> 290
 tttttttttt tcaaaacagt atatttttatt ttacaatagc aaccaactcc ccagtttggt 60
 tcaattgtga catctagatg gcttaagatt actttctggt ggtcacccat gctgaacaat 120
 attttttcaat cttccaaaca gcaaagactc aaaagagatt ctgcatttca catcagttca 180
 caagttcaag agtcttccat ttatcttagc ttttggaata aattatcttt gaggtagaag 240
 gacaatgacg aagccactta attccttggt tctgcataaa agcagattta ttcacacaaa 300
 cttcatttat gtgaataaag cagatgatga taaaatgttc tcttattctt gtttaatcag 360
 tagtggtagt gatgccagaa acttgtaaata gcacttcaaa ccaattgtgg ctcaagtgtg 420
 ngtgggtccc caaggctggt accaatgaga ctgggggtttg ggaattagtt ggtcatcatc 480
 cctcctgctg ccca 494

<210> 291
 <211> 535
 <212> DNA
 <213> Homo sapiens

<400> 291
 tcgcgtgctt aacatgaaaa caaactttgt gctgtttggt tcattgtatg cattgatgga 60
 gtcttgtctc tcacatggg gtgtctgacc atccaacctg cagtactcat aatttctcca 120
 catgcaataa tcttccaaaa tgtccaatac ccttgctcatt tgactgaaga ttagtactcg 180
 tgaacctgtt tcttttaact tagggagcag cttgtctaaa accaccattt tgccactgtt 240
 ggttactaga tgcatactg ttgtataagg tggaccaggt tctgtcccat caaagagata 300
 tggatgatta caacattttc tcaactgcat taggatgttc aataacctca ttttgtccat 360
 cttgcctgct gagttgagta tatctatatc cttcattaat atccgagtat accattccct 420
 ttgcattttt ctgaggccca catagatttt tacttccttc tttggaggca aactcttttc 480
 aacatcagcc ttaattcgac gaaggaggaa tggacgcaaa accatatgaa gcctc 535

<210> 292
 <211> 376
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(376)
 <223> n=A,T,C or G

<400> 292
 tacnagcccg tgctgatcga gatcctgggt gaggtgatgg atccttcctt cgtgtgcttg 60
 aaaattggag cctgcccctc ggcccataag cccttggttg gaactgagaa gtgtatatgg 120
 ggcccaagct actggtgccg gaacacagag acagcagccc agtgcaatgc tgtcgagcat 180
 tgcaaacgcc atgtgtggaa ctaggaggag gaatattcca tcttggcaga aaccacagca 240
 ttgggttttt tctacttggt tgtctggggg aatgaacgca cagatctggt tgactttggt 300
 ataaaaatag ggctccccca cctcccccat ttttgtgtcc tttattgnag cattgctgtc 360
 tgcaaggagg ccccta 376

<210> 293
 <211> 320
 <212> DNA
 <213> Homo sapiens

<400> 293
 tcggctgctt cctggtctgg cggggatggg tttgctttgg aaatcctcta ggaggctcct 60


```

cctcgcatgg cctgcagtct ggcagcagcc ccgagttggt tcctcgctga tcgatttctt 120
tcctccaggt agagttttct ttgcttatgt tgaattccat tgccctcttt ctcatcacag 180
aagtgatgtt ggaatcggtt cttttgtttg tctgatttat gggtttttta agtataaaca 240
aaagtttttt attagcattc tgaaagaagg aaagtaaaat gtacaagttt aataaaaagg 300
ggccttcccc tttagaatag                                     320

```

```

<210> 294
<211> 359
<212> DNA
<213> Homo sapiens

```

```

<400> 294
ctgtcataaa ctggtctgga gtttctgacg actccttggt caccaaagtc accatttcct 60
gagacttgct ggcctctccg ttgagtcacac ttggctttct gtccctccaca gctccattgc 120
caactgttgat cactagcttt ttcttctgcc cacaccttct tcgactgttg actgcaatgc 180
aaactgcaag aatcaaagcc aaggccaaga gggatgccaa gatgatcagc cattctggaa 240
tttggggtgt ctttatagga ccagaggttg tgtttgctcc accttcttga ctcccatgtg 300
agtgtccatc tgattcagat ccatgagtgg tatgggaccc cccactgggg tggaatgtg 359

```

```

<210> 295
<211> 584
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (558)
<223> n=A,T,C or G

```

```

<400> 295
cctgagttgg gctgactgcc agagacagac ccctctgggt ctcggtgaac cagccaggca 60
tttacctcag tggttggcac ctggaacctg tccagggccc tcacctgact gaggagccgc 120
cgggcagtga agtaattgtc caggctctatg ctcttgggggt ggataccata gccatccaag 180
gtattcctca ggttggtgaa ctgggtctga gtataggcag aactgggccc caggatgatc 240
tcccggagtg ggggaagctg tgaggtcagg taagtatcca cgtccaccog taccccaatc 300
aaactcagca gaatggtgaa ctggagaagt ccttccgtta agtatttctt cagagaaaagc 360
attgctgaag gaccagaatg tttatgcttt ttgggtttta aaatcttcca aaagacaaat 420
caaggccact gctctgccgc tccagccagc aggttaccct cctcagtgtc aaaccccgta 480
ccccaccctg gcagaacaca agggatgagc tccctgacgg ccccagagga aagcacaccc 540
tgtggagcca aggccaanga cacactccag accacattca cttt                                     584

```

```

<210> 296
<211> 287
<212> DNA
<213> Homo sapiens

```

```

<400> 296
ccttatcatt cattcttagc tcttaattgt tcattttgag ctgaaatgct gcattttaat 60
tttaacccaaa acatgtctcc tatcctgggt tttgtagcct tcctccacat cttttctaaa 120
caagattttta aagacatgta ggtgtttgtt catctgtaac tctaaaagat cttttttaaa 180
ttcagtctcta agaaagagga gtgcttgctc cctaagagtg tttaatggca aggcagccct 240
gtctgaagga cacttctcgc ctaagggaga gtgggtatttg cagacta                                     287

```

```

<210> 297
<211> 457
<212> DNA
<213> Homo sapiens

```

```

<400> 297
ccaattgaaa caaacagttc tgagaccggt cttccaccac tgattaagag tgggggtggca 60
ggatttaggg ataatttca tttagccttc tgagctttct gggcagactt ggtgaccttg 120
ccagctccag cagccttctt gtccactgct ttgatgacac ccaccgcaac tgtctgtctc 180

```

```

atatcacgaa cagcaaagcg acccaaaggt ggatagtctg agaagctctc aacacacatg 240
ggcttgccag gaaccatata aacaatggca gcatcaccag acttcaagaa tttagggcca 300
tcttccagct ttttaccaga acggcgatca atcttttctc tcagctcagc aaacttgcat 360
gcaatgtgag ccgtgtggca atccaatata ggggcatagc cggcgcttat ttggcctgga 420
tggttcaggga taatcacctg agcagtgaag ccagacc 457

```

```

<210> 298
<211> 469
<212> DNA
<213> Homo sapiens

```

```

<400> 298
tctttgactt tccttgtcta cctcctctgg agatctcaaa ttctccaggt tccatgctcc 60
cagagatctc aatgattcct gattctcctc ttccaggagt ctgaatgtct cttgggtcac 120
ttccacagac tccagtgggt cttgaatttc cttttctaga ggattcattg cccctgatt 180
tatttcttct ggagtccaca gtggtgcttg agtttctgga gatttcagtg tttccagggt 240
ctcttgtccc gcagacttca gtgattctag gatctctgtt tctaaagatt ttactgcctc 300
tatgctctct tctttgagtg actttaagaa ctcttgattc tcattttcaa gaggtctagc 360
tatctcctgg tcaagagact tcagtgggtc tagatccact tttctggggg gtcttaaatgt 420
catctgatcc tgttccccta gagacctccg tcgctgttga gtctctttt 469

```

```

<210> 299
<211> 165
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(165)
<223> n=A,T,C or G

```

```

<400> 299
tctgtggaga ggatgaggtt gagggaggtg gggatatntcg ctgctctgac cttaggtaga 60
gtcctccaca gaagcatcaa antggactgg cacatatgga ctcccttcac aggccacaa 120
gatgtgtctc tccttcgggc tggncggta tgcacagttg gggta 165

```

```

<210> 300
<211> 506
<212> DNA
<213> Homo sapiens

```

```

<400> 300
tctgaggaaa gtttgggctt attagtattt gctccagcga acctccaagt tttctccatt 60
gcggacaacg taactaccag ctcttggct cagtgggtcg cctccactca gaagttccca 120
gtaggttctg tcattattgt tggcacatag gccctgaata caggtgatat agggcccca 180
tgagcgctcc tccattgtga aaccaaatat agtatcatc attttctggg ctttctccat 240
cacactgagg aagacagaac catttagcac agtgacattg gtgaaatatg tttcattgat 300
tctcacagag taattgacgg agatatatga ttgtgagtca ggaggtgtca cagttatagg 360
ctcatcagcg gagatgttga agttacctga agcagagacg caagaagagt ctttgtaaat 420
atccaagaag gtctttccca tcagggcagg taagacctgg gctgcagcgt ttggattgct 480
gaatgctcct tgagaaattt ccgtga 506

```

```

<210> 301
<211> 304
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(304)
<223> n=A,T,C or G

```

<400> 301
 tcctaaggca gagccccat cacctcaggc ttctcagttc ccttagccgt cttactcaac 60
 tgcccccttc ctctccctca gaatttgtgt ttgtgcctc tatcttgttt tttgtttttt 120
 cttctggggg ggtctagaa cagtgcctgg cacatagtag gcgctcaata aatacttggt 180
 tgttgaaatgt ctctctctc tttccactct gggaaacct a ngnttctgcc attctgggtg 240
 accctgtatt tntttctggg gccattcca tttgnccagn taatacttcc tcttaaaaa 300
 ctcc 304

<210> 302
 <211> 492
 <212> DNA
 <213> Homo sapiens

<400> 302
 ttttcagtaa gcaacttttc catgctctta atgtattcct ttttagtagg aatccggaag 60
 tattagattg aatggaaaaag cacttgccat ctctgtctag gggtcacaaa ttgaaatggc 120
 tcctgtatca catacggagg tcttgtgtat ctgtggcaac agggagtttc cttattcact 180
 ctttatttgc tgctgtttaa gttgccaaac tccccctcca ataaaaattc acttacacct 240
 cctgcctttg tagttctggg attcacttta ctatgtgata gaagtagcat gttgctgcca 300
 gaatacaagc attgcttttg gcaaattaaa gtgcatgtca tttcttaata cactagaaag 360
 gggaaataaa ttaaagtaca caagtccaag tctaaaactt tagtactttt ccatgcagat 420
 ttgtgcacat gtgagagggt gtccagtttg tctagtgatt gttatttaga gagtgggacc 480
 actattgtgt gt 492

<210> 303
 <211> 470
 <212> DNA
 <213> Homo sapiens

<400> 303
 tctggggcag caggtactcc ctacggcact agtctacagg gggaaggacg ctctgtgctg 60
 gcagcgttg ctacatggc ctgtctgcac tgtaaccaca ggctgggatg tagccaggac 120
 ttggtctcct tggaagacag gtctgatgtt tggccaatcc agtccttcag accctgcctg 180
 aaacttgtat ctacgtgaa cttaaagaat aaaatgcatt tctaccccca tctcgcccc 240
 aggactggca cgacaggccc acggcagatt agatcttttc ccagtactga tcggtgcgtg 300
 gaattccagc caccacttct gattcgattc cacagtgtac ctgtcctctg agtattttaa 360
 agaagccatt gtcaccccag tcagtgttcc aggagtggc aaccagccag taggggtgtg 420
 cattctccac tccccagccc aggatgcgga tggcatggac ctcgcccgcg 470

<210> 304
 <211> 79
 <212> DNA
 <213> Homo sapiens

<400> 304
 tgtcccattg ttaactcagc ctcaaactct aactgtcagg ccctacaaag aaaatggaga 60
 gcctcttctg gtggatgcg 79

<210> 305
 <211> 476
 <212> DNA
 <213> Homo sapiens

<400> 305
 tcaactagcc accctacagc cagaagagat atgaggaaat tgtaaggaa gtcagcactt 60
 acattaagaa aattggctac aaccccgaca cagtagcatt tgtgccaatt tctgggttga 120
 atggtgacaa catgctggag ccaagtgtc acgtaagtgg ctttcaagac cattgtttaa 180
 aagctctggg aatggcgatt tcatgcttac acaaattggc atgcttgtgt ttcagatgcc 240
 ttggttcaag ggatggaaag tcacccgtaa ggatggcaat gccagtggaa ccacgctgct 300
 tgaggctctg gactgcatcc taccaccaac tcgtccaact gacaagccct tgcgcctgcc 360
 tctccaggat gctacaaaaa ttggtggtaa gttgctgtg aacaaagtgt aatttgagtt 420
 gatagagtac tgtctgcctt cataggtatt tagtatgctg taaatatatt taggta 476

<210> 306
 <211> 404
 <212> DNA
 <213> Homo sapiens

<400> 306
 tctgtctcgg agctcagggc gcagccagca cacacaggag cccacaggac agccacgtct 60
 tcacagaaac tacagaagtc aggacccagg cgaggacctc aggaacaagt gccccctgca 120
 gacagagaga cgcagtagca acagcttctg aacaactaca taataatgcg gggagaatcc 180
 tgaagaccac tgcattccac aagcactgac aaccacttca ggattttatt tcctccactc 240
 taacccccag atccatttat gagaagttag tgaggatggc aggggcatgg aggggtgaagg 300
 gacagcaagg atggtctgag ggcctggaaa caatagaaaa tcttcgtcct ttagcatatc 360
 ctggactaga aaacaagagt tggagaagag gggggttgat acta 404

<210> 307
 <211> 260
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(260)
 <223> n=A,T,C or G

<400> 307
 tctgcctan acatctgtga gggcctcaag ggctgctgcc tcgactttct ccctagctaa 60
 gtccacccgt ccagggacac agccagggca ctgctctgtg ctgacttcca ctgcagccaa 120
 ggggtcaaaat gaagcatctg cggaggccag gactccttgg catcggacac agtcaggggga 180
 aaagccaccc tgactctgca ggacagaggg tctaggggtca tttggcagga gaacactggt 240
 gtgccaaggg aagcnancat 260

<210> 308
 <211> 449
 <212> DNA
 <213> Homo sapiens

<400> 308
 tctgtgctcc cgactcctcc atctcaggta ccaccgactg cactgggcgg ggccctctgg 60
 ggggaaaggc tccacggggc agggatacat ctcgaggcca gtcatcctct ggaggcagcc 120
 caatcaggtc aaagattttg cccaactggg cggcttcaga gtttccacag aagagaggct 180
 ttcgacgaaa catctctgca aagatacagc caacactcca catgtccaca ggtgttgcac 240
 atgtggactg cagaagaact tcgggagctc ggtaccagag tgtaacaacc ttgatcgttt 300
 cggctggcaa gcctgggtgg ggtgccttgt ccagatatgt ccttaggtcc tgggtctacat 360
 gctcaaacac cagggttacc ttgatctccc gggtcagttc ggatgtggca cagacgtcca 420
 tcagccggac aacattggga tgctcaaaa 449

<210> 309
 <211> 411
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (384)
 <223> n=A,T,C or G

<400> 309
 ctgtggaaac ctgggggtgcc gggtaaattg agaactccag cttggatttc ttgccataat 60
 caactgagag acgttccatg agcagggagg tgaaccagga accagttccc ccaccaaaagc 120
 tgtggaaaac caagaagccc tgaagaccgg tgcactggtc agccagcttg cgaattcggt 180
 ccaacacaag gtcaatgatc tccttgccaa tgggtgtagtg ccctcgggca tagttattgg 240

84

```

cagcatcttc cttgcctgtg atgagctgct caggggtggaa gagctggcgg taggtgccag 300
tgcgaacttc atcaatgact gtgggttcca agtctacaaa cacagcccgg ggcacgtgct 360
tgccagcgcc cgtctcactt gaanaagggt gtttgaagga agtcatctcc t 411

```

```

<210> 310
<211> 320
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (250)
<223> n=A,T,C or G

```

```

<400> 310
tcctcgtcca gcttgactcg attagtcctc ataaggtaa caaggcagat ggtggctgac 60
cgggaaatgc ctgcctggca gtggacaaac acccttctc cagcattctt gatggagtct 120
atgaagtcaa tggcctcggt gaaccaggag ctgatgtctg ccttgtgggt gtctctccaca 180
gggatgtctt tgtactggta gtgacctca aaatggttgg gacaattggc tgagacgttg 240
atcaaggcan ttatgcccaa ggcatccagc atgtccttgc gggaagcgtg atacgcactg 300
cccaggtaca gaaagggcag
320

```

```

<210> 311
<211> 539
<212> DNA
<213> Homo sapiens

```

```

<400> 311
tctggcccat gaagctgaag ttgggagaga tgatgcttcg cctctgcttc acaaactcaa 60
aggcctcgtc cagcttgact cgattagtc tcataaggta agcaaggcag atggtggctg 120
accgggaaat gctgcctgg cagtggacaa acacccttcc tccagcattc ttgatggagt 180
ctatgaagtc aatggcctcg ttgaaccagg agctgatgtc tgccttgggt ttgtctctca 240
cagggatgct cttgtactgg tagtgacct caaaatggtt gggacaattg gctgagacgt 300
tgatcaaggc agttatgccc aaggcatcca gcatgtcctt gcgggaagcg tgatacgcac 360
tgcccaggta agaaagggc aggatttcca ccgggccacc ctgaaatcca gaaatatcca 420
acattcatca agcttgctca aagccaaggc cagtggccat acccacaaaa actttctgct 480
ggaaaagtca atttcagata ccgagtgaac tcagtctctg tgctggagga taaataaat 539

```

```

<210> 312
<211> 475
<212> DNA
<213> Homo sapiens

```

```

<400> 312
tcaaggatct tcctaaagcc accatgtgag aggattcgga cgagagtctg agctgtatgg 60
cagaccatgt cctgctgttc tagggcatg actgtgtgta ctctaaagtt gccactctca 120
caggggtcag tgataccac tgaacctggc aggaacagtc ctgcagccag aatctgcaag 180
cagcgctgt atgcaacgtt tagggcctaa ggctgtctgg tggggttggt catcacagca 240
taatggccta gtaggtcaag gatccagggt gtgaggggct caaagccagg aaaacgaatc 300
ctcaagtctt tcagtagtct gatgagaact ttaactgtgg actgagaagc attttctctg 360
aaccagcggg catgtcggat ggctgctaag gcactctgca atactttgat atccaaatgg 420
agttctggat ccagttttcg aagattgggt ggcactgttg taatgagaat cttca 475

```

```

<210> 313
<211> 456
<212> DNA
<213> Homo sapiens

```

```

<400> 313
tccacttaaa ggggtgcctct gccaaactggt ggaatcatcg ccacttccag caccacgcca 60
agcctaacaat cttccacaag gatcccgatg tgaacatgct gcacgtgttt gttctggggc 120
aatggcagcc catcgagtac ggcaagaaga agctgaaata cctgccctac aatcaccagc 180

```

85

```

acgaatactt cttcctgatt gggccgccc tgctcatccc catgtatttc cagtaccaga 240
tcatcatgac catgatcgtc cataagaact ggggtggacct ggctggggcc gtcagctact 300
acatccggtt cttcatcacc tacatccctt tctacggcat cctgggagcc ctccctttcc 360
tcaacttcat caggttctct gagagccact ggtttgtgtg ggtcacacag atgaatcaca 420
tcgtcatgga gattgaccag gaggacctcg gcccgc 456

```

```

<210> 314
<211> 477
<212> DNA
<213> Homo sapiens

```

```

<400> 314
tgctgaggct tctggaagcc tggatctgga atcattcacc agattatttc ggaaaactat 60
gcgtaccctg gtgttcttct gattggcact gactcccaca cccccaatgg tggcggcctt 120
gggggcatct gcattggagt tgggggtgcc gatgctgtgg atgcatggc tgggatcccc 180
tgggagctga agtgcccaaa ggtgattggc gtgaagctga cgggctctct ctccggttgg 240
tcctcaccca aagatgtgat cctgaagggt gcaggcatcc tcacggtgaa aggtggcaca 300
ggtgcaatcg tggaatacca cgggcctggt gtagactcca tctcctgcac tggcatggcg 360
acaatctgca acatgggtgc agaaattggg gccaccactt ccgtgttccc ttacaaccac 420
aggatgaaga agtatctgag caagaccggc cggaagaca ttgccaatct agctgat 477

```

```

<210> 315
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

```

```

<400> 315
cagggtactg atgtcaggtc tgcgaaactt ctanatttt gacctcagtc cataaaccac 60
actatcacct cggccatcat atgtgtctac tgtggggaca actggagtga aaacttcggg 120
tgctgcaggc ccgtgggaaa atcagtgacc agttcatcag attcatcaga atgggtgagc 180
tcacagact ggtgagaatc atcagtgta tctacatcat cagagtcgtt cgagtcaatg 240
g 241

```

```

<210> 316
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

```

```

<400> 316
nttntgtgat agtgtggttt atggactgag gncaaaatnt aagaagtttc gcagacctga 60
catccaancc tgcccngcgc gncgctcgaa agnncgaatt ctgcagatat ccatcacact 120
ggcggccgct cgagcatgca tctagagggc ccaattcgcc ctatantgag tnatattaca 180
attcactggc cgtcnnttta caacgtcgtg actgggaaaa ccctggcggt acccaactta 240
a 241

```

```

<210> 317
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature

```

<222> (1)...(241)
<223> n = A,T,C or G

<400> 317
aggtaccctg ctcanacagcc tgggngcctg ggttgctctcc ttgtccatcc actgggtccat 60
tctgctctgc atttttttgc tctcttttgc gaggttccac tttgggtttg ggctttgaaa 120
ttatagggtc acaantacct cgccgaaac cacnctaagg gcgaattctg cagatatcca 180
tcacactggc ggncgctcga gcatgcatct agagggccca attcgcccta tagtgagtcg 240
t 241

<210> 318
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 318
cgngnacaan ntacattgat gganggtntg nggntctgan tntttantta cantggagca 60
ttaatatattt cttnaacgtn cctcaccttc ctgaantaaa nactctgggt tgtagcgctc 120
tgtgctnana accacntnaa ctttacatcc ctcttttggga ttaatccact gcgcggccac 180
ctctgccgcg accacgctaa gggcnaattc tgcagatatc catcacactg gcgcgcgctc 240
n 241

<210> 319
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 319
caggtagctg tcggtgcgtg gaantccagc caccantntt gattcgattc cacagtgate 60
ctgtcctctg agtatatttaa agaagccatt gtcacccag tcagtgttcc aggagttggc 120
aaccagccag tagggtgtgc cattctccac tccccagccc aggatgcgga tggcatggcc 180
acccatcatc tctccggtga cgtgttggtg cctcggccgc gaccacgcta agggcgaatt 240
c 241

<210> 320
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 320
ggcaggtacc aacagagctt agtaatntct aaaaagaaaa aatgatcttt ttccgacttc 60
taaacaagtg actatactag cataaatcat tctagtataa cagctaaggc atagacattc 120
taataatttg ggaaacctg tgattacaag tgaaaactca gaaatgcaaa gatgttggtt 180
ttttgtttct cagtctgctt tagcttttaa ctctnnnaan cncatgcaca cttgnaactc 240
t 241

<210> 321

<211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)..(241)
 <223> n = A,T,C or G

<400> 321
 angtaccaac agagcttagt aattnntaaa agaaaaaat gatctttttc cgacttctaa 60
 acaagtgact atactagcat aaatcattct agtaaaacag ctaagggtata gacattctaa 120
 taatttggga aaacctatga ttacaagtga aaactcagaa atgcaaagat gttgggtttt 180
 tgtttctcag tctgctttag cttttaactc tggaagcgca tgcacacntg aactctgctc 240
 a 241

<210> 322
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 322
 ggtaccaaca gagcttagta atttctaaaa agaaaaaatg atcttttttc gacttctaaa 60
 caagtgacta tactagcata aatcattctt ctagtaaaac agctaaggta tagacattct 120
 aataatttgg gaaacctat gattacaagt aaaaactcag aaatgcaaag atgttggttt 180
 tttgtttctc agtctgcttt agcttttaac tctggaagcg catgcacact gaactctgct 240
 c 241

<210> 323
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 323
 cgagggtactg tcgtatcctc agccttggtc ttttctttta ttttagcttt acagagatta 60
 ggtctcaagt tatgagaatc tccatggctt tcaggggcta aacttttctg ccattctttt 120
 gctcttaccg ggctcagaag gacatgtcag gtgggatacg tgtttctctt tcagagctga 180
 agaaagggtc tgagctgcgg aatcagtaga gaaagccttg gtctcagtga ctcttggt 240
 t 241

<210> 324
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 324
 aggtactgtc gtatcctcag ccttggttcta tttctttatt ttagctttac agagattagg 60
 tctcaagtta tgagaatctc catggctttc aggggctaaa cttttctgcc attcttttgc 120
 tcttaccggg ctcagaagga catgtcaggt gggatacgtg tttctctttc agagctgaag 180
 aaagggtctg agctgcggaa tcagtagaga aagccttggg ctctcagtga ccttggtctt 240
 c 241

<210> 325
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 325
 gcaggtaca tttgttttgc ccagccatca ctcttttttg tgaggagcct aaatacatc 60
 ttcttggggc ccagagtcct cattcaaggc agtcaagtta agacactaac ttggcccttt 120
 cctgatggaa atatttctc catagcagaa gttgtgttct gacaagactg agagagttac 180
 atgttgggaa aaaaaaagaa gcattaactt agtagaactg aaccaggagc attaatgtct 240


```

g
<210> 326
<211> 241
<212> DNA
<213> Homo sapiens

<400> 326
gcagggtacat ttgttttggc cagccatcac tcttttttgt gaggagccta aatacattct 60
tcctgggggtc cagagtcccc attcaaggca gtcaagttaa gacactaact tggccctttc 120
ctgatggaaa tatttcctcc atagcagaag ttgtgttctg acaagactga gagagttaca 180
tgttgggaaa aaaaaagaagc attaaccttag tagaactgat ccaggagcat taagttctga 240
a 241

<210> 327
<211> 241
<212> DNA
<213> Homo sapiens

<400> 327
ggtaccagac caagtgaatg cgacagggaa ttatttcctg tgttgataat tcatgaagta 60
gaacagtata atcaaaatca attgtatcat cattagtttt ccactgcctc acactagtga 120
gctgtgccaa gtagtagtgt gacacctgtg ttgtcatttc ccacatcacg taagagcttc 180
caaggaaagc caaatcccag atgagtctca gagagggatc aatatgtcca tgattatcag 240
g 241

<210> 328
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 328
ggtacnagac caaatgaang ccacagggaa ttatttcctg tgttgataat tcatgaagta 60
gaacantata atcaaaatca attgtatcat cattagtttt ccactgcctc acactagtga 120
gctgtgccaa gtagtagtgt gacacctgtg ttgtcatttc ccacatcacg taagagcttc 180
caaggaaagc caaatcccag atgagtctca gagagggatc aatatgtcca tnatcatcan 240
g 241

<210> 329
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 329
ttcaggtcga gttggctgca gatttgtggt gcnttctgag ccgtctgtcc tgcgccaaaa 60
ngcttcaaag tattattaaa aacatatgga tcccatgaa gccctactac accaaagttt 120
accaggagat ttggatagga atggggctga tgggcttcat cgtttataaa atccgggctg 180
ctgataagaa gtaaggcttt gaaagcttca gcgcctgctn ctggtcanna ctaaccatan 240
n 241

<210> 330
<211> 241

```

<212> DNA

<213> Homo sapiens

<400> 330

```
ttttgtgcag atttgtggtg cgttctgagc cgtctgtcct gcgccaagat gcttcaaagt 60
attattaaaa acatatggat ccccatgaag ccctactaca ccaaagttta ccaggagatt 120
tggataggaa tggggctgat gggcttcacg gtttataaaa tccgggctgc tgataaaaaga 180
agtaaggctt tgaaagcttc agcgcctgct cctggtcatc actaaccaga tttacttgga 240
g                                                                241
```

<210> 331

<211> 241

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(241)

<223> n = A,T,C or G

<400> 331

```
nttttaggna ctttgggctc cagacttcac tggctcttagg nattgaaacc atcacctggn 60
ntgcattcct catgactgag gttaacttaa aacaaaaatg gtaggaaagc tttcctatnc 120
ttcnggtaag anacaaatnt nctttaaaaa aangtggaag gcatgacnta cgtgagaact 180
gcacaaactg gccactgaca aaaatgaccc ccatttgtgt gacttcattg agacacatta 240
c                                                                241
```

<210> 332

<211> 241

<212> DNA

<213> Homo sapiens

<400> 332

```
tgtgaggaga gggaacatgc tgagaaactg atgaagctgc agaaccaacg aggtggccga 60
atcttccttc aggatatcaa gaaaccagac tgtgatgact gggagagcgg gctgaatgca 120
atggagtgtg cattacattt ggaaaaaat gtgaatcagt cactactgga actgcacaaa 180
ctggccactg acaaaaatga cccccatttg tgtgacttca ttgagacaca ttacctgaat 240
g                                                                241
```

<210> 333

<211> 241

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(241)

<223> n = A,T,C or G

<400> 333

```
caggtagaag cttttttttt tttttttttt tttttttttt ttgnaaatac tntttattgn 60
aaatattcta tcctaaattc catatagcca attaatnttt acanaatntt ttgttaattt 120
ttgngngtat aaatttttaca aaaataaag gtatgtttgt tgcacacaac ttacaaataa 180
taataaactn tttattgnaa atattnttta ttgnaaatat tctttatcct aaattccata 240
t                                                                241
```

<210> 334

<211> 241

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

<400> 334
 tacctgctgn aggggntgaa gncntctctg ctgccccagg catctgcanc ccctgctgct 60
 ggttctgccc ctgctgcagc agaggagaag aaagatgaga agaaggagga gtctgaagag 120
 tcagatgatg acatgggatt tggccttttt gattaaannc ctgctcccct gcaaataaag 180
 cctttttaca caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagcttgtag ctgcccnggc 240
 g 241

<210> 335
 <211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

<400> 335
 ctatgtgctg ggatgactat ggagacccaa atgtctcana atgtatgtcc cagaaacctg 60
 tggctgcttc aaccattgac agttttgctg ctgctggctt ctgcagacag tcaagctgca 120
 gctcccccaa agctgtgct gaaacttgag ccccggtgga tcaacgtgct ccaggaggac 180
 tctgtgactc tgacatgcca gggggctcgc agcctgaga gcgactccat tcagtgggtc 240
 c 241

<210> 336
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 336
 taccaacctg tgcagccaag caacctcagc agttcccatc aaggccacct ccaccacaac 60
 cgaaagtatc atctcaggga aacttaattc ctgcccgtcc tgctcctgca cctcctttat 120
 atagtccctt cacttgattt ttttaacctt ctttttgcaa atgtcttcag ggaactgagc 180
 taatactttt ttttttcttg atgttttctt gaaaagcctt tctgttgcaa ctatgaatga 240
 a 241

<210> 337
 <211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

<400> 337
 ggtactgtat gtagctgcac tacaacagat tcttaccgtc tccacanagg tcatanattg 60
 taaatggtna atactgactt tttttttatt cccttgactc aagacagcta acttcatttt 120
 cagaactgtt ttaaactttt gtgtgctggt ttataaaata atgtgtgtaa tccttggtgc 180
 tttcctgata ccagactgtt tcccgtggtt ggtagaata tattttgntt tgatgcttat 240
 a 241

<210> 338
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 338
 aggtacaggt gtgctgctgag ccgagttttac acggaaaagga taaagcccat ttagttttctt 60
 ctcaaagtga gttttccact ttcttttgaa gtagacagca ttcaccagga tcatcctggt 120
 atccccatct acagaacctt caggtaacaa gtttgggatt ttgcctttgg tttgagtctt 180
 gacccaggaa ttaatctttt ttctagcttc ttctgcacat tctaggaagt ctactgcctg 240
 g 241

<210> 339
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 339
 taccgacggc tcctggaggg agagagtga gggacacggg aagaatcaaa gtcgagcatg 60
 aaagtgtctg caactccaaa gatcaaggcc ataaccagg agaccatcaa cggaagatta 120
 gttctttgtc aagtgaatga aatccaaaag cacgcatgag accaatgaaa gtttccgcct 180
 gtgtgtaaat ctattttccc ccaaggaaag tccttgacac gacaccagtg agtgagttct 240
 a 241

<210> 340
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 340
 gtagccctca cacacacatg cccgtaacag gatttatcac aagacacgcc tgcattgtaga 60
 ccagacacag ggcgtatgga aagcacgtcc tcaagactgt agtattccag atgagctgca 120
 gatgcttacc taccacggcc gtctccacca gaaaaccatc gccaaactcct gcgatcagct 180
 tgtgacttac aaaccttggt taaaagctgc ttacatggac ttctgtcctt taaaagcttc 240
 c 241

<210> 341
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 341
 gtaccgccta ctttcgtctc atgtctccga acttcttgct gatggccggt ccaacgttgc 60
 tgaaagctgc agttgccttt tgccctgcgt gactcagggt ttcattgtgt ttctttagg 120
 cagtggtagt ctgcatgtca tgccagcttt tgctgaagtt ctgttttaatt tcattcatca 180
 gggtcatgcc gagttttggt ttatctcaac tagatgcctt tctttcgctg acaaaacttg 240
 t 241

<210> 342
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 342
 gtacattggt gctataaata taaatgctac ttatgaagca tgaaattaag cttctttttt 60
 cttcaagttt tttctcttgt cttagcaatct gttaggcttc tgaaccaaga ccaaagtgtt 120
 acgttctct gctgcatacc aacgttactc caaacaataa aaatctatca tttctgctct 180
 gtgctgagga atggaaaaatg aaacccccac cccctgaccc ctaggactat acagtggaaa 240
 c 241

<210> 343
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 343
 gtacattggt tagcagtaat ttttttgaag caactgcact gacattcatt tgagttttct 60

```
ctcattatca gattctgttc caaacaagta ttctgtagat ccaaattgat taccagtgtg 120
ctacagactt cttattatag aacagcattc tattctacat caaaaatagt ttgtgtaagt 180
tagttttggt taccatctaa aatattttta aatgttcttt acataaaaaat ttatgttgtg 240
t                                                                 241
```

```
<210> 344
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<400> 344
ggtacaaaat tgttgaatt tagctaatag aaaaacatag taaatattta caaaaacgtt 60
gataacatta ctcaagtcac acacatataa caatgtagac aggtcttaac aaagtttaca 120
aattgaaatt atggagattt cccaaaatga atctaatagc tcattgctga gcatggttat 180
caatataaca ttaagatct tggatcaaat gttgtcccg agtcttctgc aatccagtc 240
t                                                                 241
```

```
<210> 345
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<400> 345
ggtacgaagc tgagcgcacg ggggttgccc cagcgtggag cctggacctc aaacttcacg 60
gaaaatgctc tctctctttg acaggcttcc agctgtctcc taatttcctg gatgaactct 120
ccccggcgat ttaactgac ctagaaaagt gtgagaggac tgaggaagac aaccaggtca 180
gcgttagatc ggcctctgag ggtggtgccc ttgcctgag agccaccctt taccacctg 240
g                                                                 241
```

```
<210> 346
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<400> 346
caggtaccac tgagcctgag atggggatga gggcagagag aggggagccc cctcttccac 60
tcagttgttc ctactcagac tgttgactc taaacctagg gaggttgaag aatgagacct 120
ttaggtttta acacgaatcc tgacaccacc atctatagg tcccaacttg gttattgtag 180
gcaaccttcc ctctctcctt ggtgaagaac atcccaagcc agaaagaagt taactacagt 240
g                                                                 241
```

```
<210> 347
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<400> 347
agggtacatc aaaggcatga agcactcaat tgggcaatta acattagtgt ttgttctctg 60
atggtatctc tgagaatact gggtgttaga ctggccagta gtgccttcgg gactgggttc 120
accccaggt ctgcggcagt tgtcacagcg ccagccccgc tggcctccaa agcatgtgca 180
ggagcaaatg gcaccgagat attccttctg ccactgttct cctacgtggt atgtcttccc 240
a                                                                 241
```

```
<210> 348
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
```

```

<400> 348
angtacttgg caagattnga tgctcttgng ctcantgaca tcattcataa cttgttnngtg 60
tgancagagg aggagnncat catcntgtcc tcattcgtca gnnncctctc ctctctgaat 120
ctcaaacaag ttgataatgg agaaaaattt gaattctcag gattgaggct ggactgggtc 180
cgctacang catacactag cgtggctaag gccctctgc accctgcatg anaaccctga 240
c                                                                241

```

```

<210> 349
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<400> 349
gcaggtacca tttgtctgac ctctgtaaaa aatgtgatcc tacagaagtg gagctggata 60
atcagatagt tactgtacc cagagcaata tctgtgatga agacagtgct acagagacct 120
gctacactta tgacagaaac aagtgtctaca cagctgtggt cccactcgta tatggtggtg 180
agacccaaat ggtggaaca gccttaacc cagatgcctg ctatcctgac taatttaagt 240
c                                                                241

```

```

<210> 350
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<400> 350
agggtactgt gatatttaaa atatcacagt aacaagatca tgcttgttcc tacagtattg 60
cgggccagac acttaagtga aagcagaagt gtttggtgta ctttctact taaaattttg 120
gtcatatcat ttcaaaacat ttgcatcttg gttggctgca tatgctttcc tattgatccc 180
aaaccaaadc ttagaatcac ttcatttaaa atactgagcg gtattgaata cttcgaagca 240
g                                                                241

```

```

<210> 351
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<400> 351
tacagaaatc atttggagcc gttttgagac agaagtagag gctctgtcaa gtcaatactg 60
cattgcagct tggtcactg aagaagccac gcctgagata caaaagatgc actacacttg 120
accgcgttta tgttcgcttc ctctccctt ctctctcatc aactttatta ggtaaaaaca 180
ccacatacag gctttctcca aatgactccc tatgtctggg gtttggttag aattttatgc 240
c                                                                241

```

```

<210> 352
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

```

```

<400> 352
gtaccctgtn gagctgcacc aagattannt ggggccatca tgactgcanc cacnacgang 60
acgcaggcgt gnagtgcac gtctgaccg gaaaccctt cacttctctg ctcccagggt 120
gtcctcnggc tcatatgtgg gaaggcanan gatctctgan gagttnctg gggacaactg 180
ancagcctct ggagaggggc catataataa gctcaacatc attggcaaaa aaaaaaaaaa 240
a                                                                241

```

```

<210> 353

```

94

<211> 241
<212> DNA
<213> Homo sapiens

<400> 353
aggtaccagt gcattaat ttt gggcaaggaa agtgtcataa tttgatactg tatctgtttt 60
ccttcaaagt atagagcttt tggggaagga aagtattgaa ctgggggttg gtctggccta 120
ctgggctgac attaactaca attatgggaa atgcaaaagt tgtttgata tggtagtg 180
tggttctctt ttggaat tttcagggtga ttttaataata atttaaaact actataaaaa 240
c 241

<210> 354
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 354
ngcaggtccg ggcaggtacc aagattcatt ctcatcaaaa actagaaaca gaagggcaaa 60
ttccagtttc cttctgggat tgaatacttt caagtaaggt cttcgacaaa caatcagggg 120
gccaaattaat ccactgtaga ggtccttaac ttgatccaca gttgaataat aagcccatgg 180
aatacaagca gaatcctctg ttccagctcc agatctttct gggattttcc atacgtaagt 240
g 241

<210> 355
<211> 241
<212> DNA
<213> Homo sapiens

<400> 355
ggtaccacc ctaaatttga actcttatca agaggctgat gaatctgacc atcaaatagg 60
atagatgga cttttttttg agttcattgt ataaacaaat tttctgattt ggacttaatt 120
cccaaaggat taggtctact cctgctcatt cactctttca aagctctgtc cactctaact 180
tttctccagt gtcatagata gggaattgct cactgcgtgc ctagtctttc ttcacttacc 240
t 241

<210> 356
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 356
aggtactgta attgagcatc cggaatntgg agaagtaatt tagctacagg gtgaccaacg 60
caagaacata tgccagttcc tcgtagagat tggactggct aaggacgatc agctgaagg 120
tcatgggttt taagtgcttg tggctcactg aagcttaagt gaggatttcc ttgcaatgag 180
tagaatttcc cttctctccc ttgtcacagg tttaaaaacc tcacagcttg tataatgtaa 240
c 241

<210> 357
<211> 241
<212> DNA
<213> Homo sapiens

<400> 357
ttttgtacca cccgatgat caaggaaaat tctgcccatt tttatggctg aagtttctaaa 60
aacctaattc aaagttcttc catgatccta cactgcctcc aagatgggcc aggcctggcat 120
aaggcctgag cggcggtgag atccgcggct gccagcagct tgcgcctctt cagctggtat 180
gaagcccctc ggccaccga gtctccagga cctgcccggg cgcgcctcga aagggcgaat 240
t 241

<210> 358
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 358
aggtacgggg agtgggggtg aagcntgttc tctacatagg caacacagcc gcctaantca 60
caaagtcagt ggtcggccgc ttcgaccaac atgtggtgag cattccacgg gcgcatgaag 120
tctgggtgct gtgctcgagt ctctgaatat tttgatagga agcgacaaga aaattcaaac 180
tgctctttgc tgactactgg aaagtgaata gatgctcaag tttaccattc aaagaaacca 240
t 241

<210> 359
<211> 241
<212> DNA
<213> Homo sapiens

<400> 359
gaggtacaca aaaggaatac cttctgagag ccagggagtg aggaaagggg aaggagactt 60
gacgtcaagg gtgcttttga ggaacatgac gggccagcca gcctgcccc aacttgaggc 120
cctgctgggc tcttgtgact ataaatatac tgtctatttc taatgcaatc cgtctttcct 180
gaaagatcct gttatctttt actattgaga catgctttca tttttgtggt cctggtttcca 240
a 241

<210> 360
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 360
ngtactctat actaattctg cttttttata cttaattcta aattttctccc ctctaattta 60
caacaaattt tgtgattttt ataagaatct atgcctcccc aattctcaga ttctttctctt 120
ttctccttta tttctttgct taaattcagt ataagctttc ttggtatttt aggcttcagt 180
cacattctta ttcctaaaca ccagcagttc ttcagagacc taaaatccag tataggaata 240
a 241

<210> 361
<211> 241
<212> DNA
<213> Homo sapiens

<400> 361
aggtactctc cgtgccccga cactgaacat tatccagcca gatctgccca gtgccagctc 60
ccactttgta cttttcttac tatcctgtct agaactcatgt cttatgattt taacagatat 120
agaaccactc ctgaaaaatg ttcttttact ttctcgtttc cttttttaatc tatcatcctg 180

actactgaac ttaaaatctt tttcttccct tttttgtttc ttttttcttt tatcctgttc 240
a 241

<210> 362
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 362
aggtactttt atacctngct tangtcagtg acagatttac caatgacaac acaattttta 60
aattccaaca catatattac tttgtcctat gaagggcata aagtcaatat attttaaatt 120
ttaaaaaacag aatggatata atgacctttt tacacatcag tgatatttaa aagacttaaa 180
gagacaatac tatggttgag aactgggctt cctattccag ccctaattaa agaaaaata 240
g 241

<210> 363
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 363
ttangtacta aaaacaaaat cctaattctg ttttaaagag ctgggagatg ttaatcatat 60
gctcagtttt tccacgttat aatttcctaa atgcaaaactt ttcaatcagg gcagttcaaa 120
ttcattacat cacagtaaata aacagtagcc aactttgatt ttatgcttat aggaaaaaaa 180
atcctgtaga tataaaaaaca gcaaattttg acaataaaaa ctcaaaccat tcatccctaa 240
a 241

<210> 364
<211> 241
<212> DNA
<213> Homo sapiens

<400> 364
ggtacaagca gttagtctctg aaggcccttg ataagaatgt catcttctcc ccaactgagca 60
tctccaccgc cttggccttc ctgtctctgg gggcccataa taccaccctg acagagattc 120
tcaaaggcct caagttcaac ctcacggaga cttctgaggc agaaattcac cagagcttcc 180
agcacctcct gcgcaccctc aatcagtcca gcgatgagct gcagctgagt atgggaaatg 240
c 241

<210> 365
<211> 241
<212> DNA
<213> Homo sapiens

<400> 365
cgaggtagtg agattacagg catgagccac cagcccggc caaaaacatt taaaaaatga 60
ctgtccctgc tcaaaacttg cagtaggaaa tgtaatttga catatatcac ttccagaaaa 120
aaactttaaa tctttctata aaatgaattt gatacatcat cagcatgaag tgaagttaaa 180
atctcttaca aagtaaattc aggtatatca acaatgagat ccaaaagtat cggttcaaga 240
t 241

<210> 366

<211> 241
 <212> DNA
 <213> Homo sapiens

<400> 366
 ggcagggtaca catcaaacac ttcatgtcct aaatgcaggg acatgcttcc atctgaccac 60
 ttgactatcc gagcattgct ttctttaatt tcatttcctt cttcatctcg gcgtatcctc 120
 catcttatag tattttctac cttaaatttt aacctgggtc taccttcttc atccagcatt 180
 tcttcactctt caaattcctc ttcataatac tgggctctac acttgagaaa gttgggcagt 240
 t 241

<210> 367
 <211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

<400> 367
 gcagggtacaa ataattcctg ttgtnacatt tagtggacgc gattatctgt atacctcaaa 60
 ttttaattta agaaagtatc acttaaagag catctcatit tctatagatt gaggcttaat 120
 tactgaaaag tgactcaacc aaaaagcaca taacctttta aaggagctac acctaccgca 180
 gaaagtcaga tgccctgtaa ataactttgg tctttcaaaa tagtggcaat gcttaagata 240
 c 241

<210> 368
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 368
 tttgtacatt gttaatagtg accctcggag gaaatggatt tctcttctat taaaaactct 60
 atgggtatata agcattacat aataatgcta cttaaccacc ttttgtctca agaattatca 120
 ccaaagtttt ctggaaataa gtccacataa gaattaaata tttaaaagggt gaaatgttcc 180
 ttatttttaac tttagcaaga tcttttcttt ttcattaaga aacactttaa taatttttaa 240
 g 241

<210> 369
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 369
 gcagggtactt tattcttatt tcttatccta tattctgtgt tacagaaaaa ctactaccat 60
 aaacaaaaca ccaaccagcc acagcagttg tgtcaagcat gacaattgggt ctagtcttca 120
 cattttatta gtaagtctat caagtaagag atgaagggtc tagaaaaacta gacacaaagc 180
 aaccagggtc caaatcacca aggtagatct gtgcttagct aaagggaac acccgaagat 240
 t 241

<210> 370
 <211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

```

<400> 370
ngttcacagt gccctccgg cctcgccatg aggctcttcc tgtcgctccc ggtcctgggtg 60
gtggttctgt cgatcgtctt ggaaggccca gcccagccc aggggacccc agacgtctcc 120
agtgccttgg ataagctgaa ggagtttgga aacacactgg aggacaaggc tcgggaactc 180
atcagccgca tcaaacagag tgaactttct gccaaagatgc gggagtgggtt ttcagaagac 240
a                                                                                   241

```

```

<210> 371
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

```

```

<400> 371
ggcaggtcat cttgagcctt gcacatgata ctcagattcc tcacccttgc ttaggagtaa 60
aacaatatac ttacagggt gataataatc tccatagtta tttgaagtgg cttgaaaaag 120
gcaagattga cttttatgac attggataaa atctacaaat cagccctcga gttattcaat 180
gataactgac aaactaaatt atttccctag aaaggaagat gaaaggnagt ggagtgtgggt 240
t                                                                                   241

```

```

<210> 372
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

```

```

<400> 372
aggtagcagca aagcgaccct tgggtgnata gatcagacgg aaattctctc ccgtcttgnc 60
aatgctgatg acatccatga atccagcagg gtaggttata tcagttcgga ccttgccatc 120
gatttttaatg aaccgctgca tgcaaatctt ctttacttca tctcctgtca gggcatactt 180
aagtctgttc ctcaggaaaa tgatgagggg gagacactct ctcaacttgt ggggaccgggt 240
g                                                                                   241

```

```

<210> 373
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<400> 373
tactgaaaca gaaaaaatgt attcccacaa aagctgttac acagcggttt cccgtcccca 60
gaagcagtag aaaatcttag cattccaatg gaaggcatgt atttgtaaaa tattctaaaa 120
tcagctctat agtttccttg tcctctttga taagggatca gacagagggt gtgtccccct 180
tcagcagcta cccttcttga caaactggtc tccaataata cctttcagaa acttacaaga 240
c                                                                                   241

```

```

<210> 374
<211> 241
<212> DNA
<213> Homo sapiens

```

```

<400> 374
caggtactaa aacttacaat aaatatcaga gaagccgtta gtttttacag catcgtctgc 60
ttaaaagcta agttgaccag gtgcataatt tcccatcagt ctgtccttgt agtaggcagg 120
gcaatttctg ttttcatgat cggaatactc aaatatatcc aaacatcttt ttaaaacttt 180

```

gatttatagc tcctagaaag ttatgttttt taatagtcac tctactctaa tcaggcctag 240
c 241

<210> 375
<211> 241
<212> DNA
<213> Homo sapiens

<400> 375
aggtacaaag gaccagtatc cctacctgaa gtctgtgtgt gagatggcag agaacgggtgt 60
gaagaccatc acctccgtgg ccatgaccag tgctctgccc atcatccaga agctagagcc 120
gcaaattgca gttgccaata cctatgcctg taaggggcta gacaggattg aggagagact 180
gcctattctg aatcagccat caactcagat tgttgccaat gccaaaggcg ctgtgactgg 240
g 241

<210> 376
<211> 241
<212> DNA
<213> Homo sapiens

<400> 376
ggtacatttt actttccttc tttcagaatg ctaataaaaa acttttgttt atacttaaaa 60
aaaccataaa tcagacaaac aaaagaaacg attccaacat cacttctgtg atgagaaaaag 120
aggcaatgga attcaacata agcaaagaaa actctacctg gaggaagaa atcgatcagc 180
gaagaaacaa ctcggggctg ctgccagact gcaggccatg cgaggaggag ctcctagag 240
g 241

<210> 377
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 377
tcctttctgt ccaggtgatt cacagactag acctttctta tcctcctcct agagttttga 60
cttgggactc tagtgtaag atgatgagcc cgtgcatcag gtccttctgc actttgggtg 120
aagtctccca gggtaggttt cctatttgaa acagtggaat catgtttcca gtgataaagt 180
ttaatgacct catccttttt tttttttttc tcatctgcca tttgtgtgtc ttanatgggt 240
t 241

<210> 378
<211> 241
<212> DNA
<213> Homo sapiens

<400> 378
aggtcagcga tcaggtcctt tatgggcagc tgctgggcag cccacaagc ccagggccag 60
ggcactatct ccgctgcgac tccactcagc ccctcttggc gggcctcacc ccagcccca 120
agtcctatga gaacctctgg ttccaggcca gccccttggg gaccttggtg accccagccc 180
caagccagga ggacgactgt gtctttgggc cactgctcaa cttccccctc ctgcagggga 240
t 241

<210> 379
<211> 241
<212> DNA
<213> Homo sapiens

<400> 379

100

```
tacggagcaa tcgaagaggc atatccacac ttgggggtggc tatagggtctg gaaaatgctg 60
aagatgactg ctttcactga gggtcaaggat tgtaatatgg ccagctttgt aaagccatta 120
aagcagaagt ttcttcagt atcttctctc taagaaacac catcacctcc atgtgcctta 180
cagaggcccc ctgcgttctg ctgcattgct tttgcgcaat cccttgatga tgaagatggt 240
c 241
```

```
<210> 380
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
```

```
<400> 380
acgtacacgc agaccgacat gggnnnttca ggcntnagat caaactcaaa acctgnaatg 60
atatccactc tctttttctt aagctcaggg aaatatccca agtagaagtc canaaagtca 120
tcggctaana tgcttcngaa tttgaattca tgcacatagg ccttgaaaaa actgtcaaac 180
tgannctgat caccaccaa gtgggccntn tatgacacaa agcagaaaacc tttctcntan 240
g 241
```

```
<210> 381
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<400> 381
aggtacaact taatggatta gcttttgggt ttaactgaat atatgaagaa attgggtctg 60
tctaaagaga gggatatttc tatggctttt agttcacttg tttgtatttc atcttgattt 120
ttttctttgg aaaataaagc attctatttg gttcagattt ctcagatttg aaaaaggctc 180
tatctcagat gtagtaaatt atttcctttc agtttgtgaa agcaggattt gactctgaaa 240
g 241
```

```
<210> 382
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<400> 382
gtactgctat aatcaatacg tctgatagac aggtttatcc actatattga ccctacctct 60
aaaaggattg tcataattta tatgctttat gtttacacct atgatacagt tgccttgga 120
cacaaaattt ttcattgtaa ttaaaaaaag aagagttgtg cagacagaag aaatcaaattc 180
taagaaaatc acaggagtag ataaatactc tagaattcat atacccttgg aagatggggtt 240
t 241
```

```
<210> 383
<211> 241
<212> DNA
<213> Homo sapiens
```

```
<400> 383
ggcagggtaca aagtcttctc tttgcttttt ataattttaa agcaaataac acatttaact 60
gtattttaagt ctgtgcaa atccttcag aagaaatc caagattctg tttgcagagg 120
tcattttgtc tctcaaagat gattaaatga gtttgtcttc agataaagtg ctctgtcca 180
gcagaactca aaaggccttc aagctgttca gtaagtgtag ttcagataag actccgtcat 240
a 241
```

```
<210> 384
<211> 241
<212> DNA
```

101

<213> Homo sapiens

<400> 384

```
ggtacacaaa atacacttgc aagcttgctt acagagacct gttaaacaaa gaacagacag 60
attctataaa atcagttata tcaacatata aaggagtgtg attttcagtt tgttttttta 120
agtaaataatg accaaactga ctaaataaga aggcaaaaca aaaaattatg cttccttgac 180
aaggcctttg gagtaacaaa aatgctttta ggctcctggt gaatggggtt gcaaggatga 240
a                                                                 241
```

<210> 385

<211> 241

<212> DNA

<213> Homo sapiens

<400> 385

```
ggcaggtcta caatggctct gtcccttctg tggaatcggt acaccaagag gtctcagtcc 60
tggtccctga cccacagtg agctgtttag atgatccttc acatcttcct gatcaactgg 120
aagacactcc aatcctcagt gaagactctc tggagccctt caactctctg gcaccaggta 180
ggtttgaggg ctatgtccct ttaacttatc catgcagagt agccaaactt tacctgaaag 240
a                                                                 241
```

<210> 386

<211> 241

<212> DNA

<213> Homo sapiens

<400> 386

```
aggtagcttt ttcctctcca aaggaacagt ttctaaagtt ttctgggggg aaaaaaaact 60
tacatcaaat ttaaaccata tgtaaactg catattagtt gtgttacacc aaaaaattgc 120
ctcagctgat ctacacaagt ttcaaagtca ttaatgcttg atataaattt actcaacatt 180
aaattatctt aaattattaa ttaaaaaaaaa aactttctaa gggaaaaata aacaaatgta 240
g                                                                 241
```

<210> 387

<211> 241

<212> DNA

<213> Homo sapiens

<400> 387

```
acccactggg ccgctgtgga gtatctccac tctccctctg tgagggccgc tcccaccgac 60
cagtcgaact ttcgtaaatg gagttaatgt gtttccactc cccttttccc ctttctggcc 120
ttttggtcca gaatttctct gccttccggc atatcctggg agtcctcgac ttccaggaaa 180
gccaatgctt ccccgatcac ctttaagacc cggaggacct attggacctg gaaatcctcg 240
t                                                                 241
```

<210> 388

<211> 241

<212> DNA

<213> Homo sapiens

<400> 388

```
tttgtactct tgtccacagc agagacattg agtataccat tggcatcaat gtcaaaagtg 60
acttcaatct gaggaacacc tcgggggtgca ggaggtatgc ctgtgagttc aaacttgcca 120
agcaggttgt tatcctttgt catggcacgc tcgccttcat aaacctgaat aagtacacca 180
ggctggttgt cagaataggt agtgaaggtc tgtgtctgct tggtaggaat ggtggtatta 240
c                                                                 241
```

<210> 389

<211> 241

<212> DNA

<213> Homo sapiens

102

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 389
tacctntggt agtgagcacc ttgtcttntg tgcttatntc ttnaagataa atacatggaa 60
ggatgtgaaa atcggaacac caactatgtg tctcactgca tctaagttaa gcagccacag 120
ctgtgagagt tttcaaagca gaaagatgct gatgtgacct ctggaattca gacatactga 180
gctatgggtc agaagtgttt tacttaaaaa gcaaacaatc cccaggaaat actgaatagg 240
a 241

<210> 390
<211> 241
<212> DNA
<213> Homo sapiens

<400> 390
gcaggtacat ccacatgttc ctccaaatga cgtttggggt cctgcttgcc aacattcttt 60
attgccagct gtccaggtgt catcttatct tcttcttcta cagccttatt gtaattcttg 120
gctaattcca acatctcttt taccactgat tcattgctt tacaatgttc actgtagtcc 180
tgaagtgtca aaccttccat ccaactcttc ttatgcaaat ttagcaacat cttctgttcc 240
a 241

<210> 391
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 391
cnggcacaa cttntgtttt tnntnttttt tttttttttn tctttatttn tttttantnt 60
taaaaaaaa nnntannnaa annngggttt aaatnctntn nncagancat taaaactgaa 120
ggggaaaaaa aaacaaaaaa cgagcttntt anttnacntg ggnttggggn gntgctgatn 180
tnaagaagca anntttanan cnngcnnnat ganngagngn tcannttgaa atttnnacc 240
t 241

<210> 392
<211> 241
<212> DNA
<213> Homo sapiens

<400> 392
gaggtactaa atggtatcct tagattaaaa ttttgtgctt gataacagct gttttttcta 60
cattagaaat aagatgccac acaaggaact acattccaga tttaaagaaa tgaaaggata 120
ccattagtgt gtataacaga ttattgttca tacttgtaaa gcatcttatg tcattgagaa 180
tataaagaac agtgccttag aagacagtga aaggtaagct ctagcttaat gtctatgatt 240
t 241

<210> 393
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

103

<400> 393
ggcaggtaca taagcataat cagttatgga cagcttcttg tataaattgc tattcancaa 60
tacataaact gcctnaaaga tttatgctta caggtagaca ttcaatttac caataaaaca 120
gcatgttctg aaaatatggg cacattttaa aacatattaa gacagttctg ttaaccataa 180
tagtcccaca gtatgactga gtaataagaa tctacttcaa aagnaaaaaa aaaattaatc 240
a 241

<210> 394
<211> 241
<212> DNA
<213> Homo sapiens

<400> 394
aggtagacga gcagtagatg gctgcaacaa ccttcctcct accccagccc agaaaatatt 60
tctgcccac cccaggatcc gggaccaaaa taaagagcaa gcaggcccc ttactgagg 120
tgctgggtag ggctcagtgc cacattactg tgctttgaga aagaggaagg ggatttggtt 180
ggcactttaaa aaatagagga gtaagcagga ctggagaggc cagagaagat accaaaattg 240
g 241

<210> 395
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 395
nggcnggnnc caanatatga aatntnanta tnatacatga tnaaaagctt tatntatttt 60
agtgaagtaat taagttttaca ctgtgaataa ggattaattc ccagatgacc atctacagtt 120
actaccacat agaggggtata cacggatgga tcgattacaa gaatataaaa cttattttcc 180
ttcctgtatc cacattttctt tgcaatgtga atttgcaggc cctctcaaga agtggagtct 240
a 241

<210> 396
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 396
gaggtacacc ttgaatgaca atgctnggag cccccctgtg gtcacgacg cctccactgc 60
cattgatgca ccatccaacc tgcgtttcct ggccaccaca cccaattcct tgctgggtatc 120
atggcagccg ccacgtgccca ggattaccgg ctacatcatc aagtatgaga agcctgggtc 180
tcctcccaga gaagtgggtcc ctcggccccg cctgggtgtc acagaggcta ctattactgg 240
c 241

<210> 397
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)

104

<223> n = A,T,C or G

<400> 397

```
ggcagggtacc agcaggggga tgtgtttctg gggaattgtg gctctggaag cttcacgggt 60
tcccagaatg tggaaaatat atctgtgcan gatagaaatc ctgcccagag gctgtttctg 120
tctcatttga gctctccttc atgtggcaga gctgactgtg gcggtttagg agcctacatt 180
ttagaaaagc ttacctcaaa gttctgcatt gagcctgagc actggaaaag agataaaaata 240
a                                                                 241
```

<210> 398

<211> 241

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(241)

<223> n = A,T,C or G

<400> 398

```
gangtgacca ngacatcacc tnacacntgg aaagcganga nttgaatggt gcntacaang 60
ccntaccnt tgcccannac ctgaacgcgc cttntgattg ggacagccgt gggaaggaca 120
gttatgaaac nantcanctg gatgaccana gtgntgaaac cnacanncac angcnntcna 180
cattatataa ncggaaagct aatgatgaga gcaatgatca ttccgatgtn attgatagtc 240
a                                                                 241
```

<210> 399

<211> 241

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(241)

<223> n = A,T,C or G

<400> 399

```
cagagtgaga tgggagtggg agggccaatc tgatacagaa ggggggtgaag ggtagggccc 60
ctgagcagcc cacccttac cctgacgaag gcaatcctcc tctggaatgt ctcttccctc 120
ttcagttctg gttctgcctc agccacgaac tgggaaggag tgaggaacat cccaacggca 180
atgagagtat cccagtgtact ccaaacagga angaatcagt gttcanaaag tcaggggcct 240
t                                                                 241
```

<210> 400

<211> 241

<212> DNA

<213> Homo sapiens

<400> 400

```
ggtactcttg ctcttttagc tagagtgtat gtgaaaataa agaaatacat cattgtattc 60
acaaccatgt gtcttcattt ataacttttt gtttaaaaaa ttttttagttc aagtttagtt 120
cattgatatt atcctctgaa tgcagttaag gctgggcaga aattctactc atgtgacatc 180
tgccacaggc ctattttgaa gcttttcttc taatgggcaa tgtttgcct taccaggatt 240
t                                                                 241
```

<210> 401

<211> 241

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

105

<222> (1)...(241)
 <223> n = A,T,C or G

<400> 401
 nncagggtact ttgtagagca gagagaggct ttgggttcctc ctttcttcaa tcacgtggag 60
 atgtgtcatc acctgggatt tcatctgggc cgccttttct gggccaacag ccaacacatg 120
 ctggtaataga cggatgggat gtaagcgatc tttgttctca gcacggacat aacgccgtaa 180
 ggcttgagga atgcgatgag gccgtggcgg gtcagactgc aaggcagcca ggtagttctc 240
 c 241

<210> 402
 <211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

<400> 402
 ggcagggtcca aaaaaaacct aaaaanngtt tcaggaatgt agagaaatat ccaacttaaa 60
 tagcgaaaaa gtgcaccata attactgctg cactgcagtc atttctgcaa ttcccatgtt 120
 tcttaataaa ctatcttggtc agataacaca caatataaag agcaattatg aaaaacagac 180
 atttacatat acttctaaag tcttattggg aatatcctgt ttggccattg ggataaccaa 240
 t 241

<210> 403
 <211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

<400> 403
 aggtgttaac taccgctcc gagacgggat tgatgacgag tcctatgang ccattttcaa 60
 gccggtcatg tccaaagtaa tggagatgtt ccagcctagt gcggtggtct tacagtgtgg 120
 ctcagactcc ctatctgggg atcggttagg ttgcttcaat ctaactatca aaggacacgc 180
 caagtgtgtg gaatttgtca agagctttaa cctgcctatg ctgatgctgg gaggcgggtg 240
 t 241

<210> 404
 <211> 241
 <212> DNA
 <213> Homo sapiens

<400> 404
 cagggtactgc aaccataaa atactgtttc ctcataattc accttcctta atttggagtt 60
 ttctgtcttc ttttcacggc attcaaagta ggaataaaact ttgcttgtgt tgggtggata 120
 ttgtttatag tgagtaacct tgtaggagtc ggtggccagg aggatgttga actcggcttc 180
 tgcccgagga ttcatctcgg gccggaggac aaggggcccg cgcgccgcga gctccctgac 240
 c 241

<210> 405
 <211> 266
 <212> DNA
 <213> Homo sapiens

<400> 405

106

```
ttctgggctg gggagtggag agaaagaagt tgcagggctt acaggaaatc ccagagcctg 60
aggttttctc ccagatttga gaactctaga ttctgcatca ttatctttga gtctatattc 120
tcttgggctg taagaagatg aggaatgtaa taggtctgcc ccaagccttt catgccttct 180
gtaccaagct tgtttccttg tgcacacctc ccaggctctg gctgcccctt attggagaat 240
gtgatttcca agacaatcaa tccaca                                     266
```

<210> 406
<211> 231
<212> DNA
<213> Homo sapiens

```
<400> 406
ttggtgaaga accattcctc ggcacacctg cggttcttct ctgccatctt ctcatactgg 60
tcacgcatct cggtcagaat gcggtcagc tccacgccag gtgcagcgtc catctccaca 120
ttgacatctc caccacactg gcctctcagg gcattcatct cctcctcgtg gttcttcttc 180
aggtaggcca gtcctcctt caggctctca atctgcatct ccaggtcagc t          231
```

<210> 407
<211> 266
<212> DNA
<213> Homo sapiens

```
<400> 407
cagcatcatt gtttataatc agaaactctg gtccttctgt ctggtggcac ttagagtctt 60
ttgtgccata atgcagcagt atggaggag gattttatgg agaaatggg atagtcttca 120
tgaccacaaa taaataaagg aaaactaagc tgcattgtgg gttttgaaa gggtattata 180
cttcttaaca attctttttt tcagggaact ttctagctgt atgactgtta cttgaccttc 240
tttgaagaagc attcccaaaa tgctct                                     266
```

<210> 408
<211> 261
<212> DNA
<213> Homo sapiens

```
<400> 408
ctgtgtcagc gagcctcggg acactgattt ccgatcaaaa gaatcatcat ctttaccttg 60
acttttcagg gaattactga actttcttct cagaagatag ggcacagcca ttgccttggc 120
ctcacttgaa ggtctgcat ttgggtcctc tggctctctg ccaagtttcc cagccactcg 180
aggagtaat atctggaggg caaagaagag acttatgtta ttgttgaacc tccagccaca 240
gggaggagca tggcagtggt t                                     261
```

<210> 409
<211> 266
<212> DNA
<213> Homo sapiens

```
<400> 409
gctgacagta atacactgcc acatcttcag cctgcaggct gctgatgggt agagtgaat 60
ctgtcccaga cccgctgccg ctgaatcggg cagggatccc ggattcccgg gtagatgcc 120
agtaaagtga cagtttagga ggctgtcctg gttctctctg gtaccaagct aagtagttct 180
tattgttga gctgtctaaa acactctggc tggctcttga gttgatgggt gccctctcgc 240
ccagagacac agccaggag tgtgga                                     266
```

<210> 410
<211> 181
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

```

<400> 411
gccctggcgag tacttggccg atgtggacac ctctgatgag gaaagcatcc gggctcacgt 60
gatggctctc caccattcca agcggagagg cggggcgtct tctgagagtc agggctctagg 120
tgctggagtg cgcacggagg ccgatgtaga ggaggaggcc ctgaggagga agctggagga 180
gactggccagc aacgtcagtg accaggagac ctctgccgag gaggaggaag ccaaggacga 240
aaaggcgagc ccaacacagg a
261

```

```
<220>  
<221> misc_feature  
<222> (1)...(241)  
<223> n = A,T,C or G
```

```
<400> 412
ntttntctt tacaattcag ttttcaaca cttgagagct ttcttcatgt tgncagcaa 60
cagagctgta tctgcaggnt cgtaagcata naqacngttt gaatatcttc canggatatc 120
ggctctaact gncagagatg ggtcaacaaa cataatcctg qggacatact g 171
```

```
<210> 413
<211> 266
<212> DNA
<213> Homo sapiens
```

<400> 413						
tttagagccaa	agatagcatc	aactgtat	gaaggaactg	tagtttgcg	attttatgac	60
atttttataa	agtactgtaa	ttctttcatt	gaggggctat	gtgatggaga	cagactaact	120
cattttgtta	tttgcattaa	aattat	ggtctctgtt	caaatagagt	tggagaatgc	180
ttgacttg	ggtctgtgta	aatgtgtata	tatatatacc	tgaatacagg	aacatcgga	240
acctattcac	ttccacacac	ctctgct				266

```
<210> 414
<211> 266
<212> DNA
<213> Homo sapiens
```

```
<220>  
<221> misc_feature  
<222> (1)...(241)  
<223> n = A,T,C or G
```

<400>	414							
tttgcatataa	ttgagtgaaa	agtggcagat	ggcattaact	ctgctccgct	tcaagctggc		60	
tccatgacca	ctcaaggcct	cccancctg	ttcgtcaagt	tgtcctcaag	tccaagcaat		120	
ggaatccatg	tgtttgcaaa	aaaagtgtgc	tanttttaag	gnctttcgta	taagaatnaa		180	
tganaacaatt	ttcctaccaa	aggangaaca	aaaggataaa	tataatacaa	aatatatgta		240	
tatggtttgt	tqctacaatta	tataaac					266	

108

<210> 415
<211> 266
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 415
cctccatcca gtctattaat tgttgccggg aagctanagt aagtagttcg ccagttaata 60
gtttgcgcaa cgttggttgc attgctacag gcacgcgtgg gtnacgctcg tcgattggta 120
tggcttcatt cagctccggg tcccaacgat caaggcgagt tacatgatcc cccatgttgt 180
gcaaaaaagc ggtagctcc ttgggtcctc cgatcggtgt canaagtaag ttggccgcag 240
tggtatcact catggttatg gcagca 266

<210> 416
<211> 878
<212> DNA
<213> Homo sapiens

<400> 416
cctgacgata gccatggctg taccacttaa ctatgattct attccaactg ttcagaatca 60
tatcacaaaa tgacttgtac acagtagttt acaacgactc ccaagagagg aaaaaaaaaa 120
aaaaagacgc ctcaaaaattc actcaacttt tgagacagca atggcaatag gcagcagaga 180
agctatgctg caactgaggg cacatatcat tgaagatgtc acaggagttt aagagacagg 240
ctggaaaaaa tctcatacta agcaaacagt agtatctcat accaagcaaa accaagtagt 300
atctgctcag cctgccgcta acagatctca caatcaccaa ctgtgcttta ggactgtcac 360
caaagtcaga ttcggtgcta accaggtggc atctatgatc aacgtcgccc ctcttattta 420
acaaagggct ctgaaggagg tgttctccaa gcaacaagga gactgcttca gtacaagact 480
ttgcaccttg aattcaattg catcaagtgt ggatagcaaa ataagtatct taccattgaa 540
atatgtgttc agcctaagat tttaccacc accagaacaa aagtgagggg gagagggatg 600
ggccagtgag gggatggggg agaaaaaaaa atcacaggat taccaccaa gcctgtgttt 660
aaaagggctc ccttcactat tcaggaaggg aagtgggaagg agaaattaac caattcctgc 720
cacagcagcc ctttttggtc gcttccacaa tagatacttt atggagtggc acagccaacc 780
ctatctgtga cctgccctgc ggataaacac agccaagcag gtttaattag atcaaagaca 840
caaagggcta ttccctcctt tcataacaac gcagacct 878

<210> 417
<211> 514
<212> DNA
<213> Homo sapiens

<400> 417
ttctgacttc tagaagacta aggctggtct gtgtttgctt gtttgccac ctttggctga 60
taccagaga acctgggcac ttgctgcctg atgcccacc ctgccagtca ttctccatt 120
caccagcgg gaggtgggat gtgagacagc ccacattgga aaatccagaa aaccgggaac 180
agggatttgc ccttcacaat tctactccc agatcctctc ccctggacac aggagacca 240
cagggcagga ccctaagatc tggggaaagg aggtcctgag aaccttgagg tacccttaga 300
tccttttcta ccacttttc tatggaggat tccaagtcac cacttctctc accggcttct 360
accaggttcc aggactaagg cgttttctcc atagcctcaa cattttggga atcttccctt 420
aatcacctt gctcctcctg ggtgcctgga agatggactg gcagagacct ctttgttgcg 480
ttttgtgctt tgatgccagg aatgccgctt agtt 514

<210> 418
<211> 352
<212> DNA
<213> Homo sapiens

<400> 418

109

```

ctgcaccagc gattaccagt ggcattcaaa tactgtgtga ctaaggattt tgtatgctcc 60
ccagtagaac cagaatcaga caggtatgag ctagtcaaca gcaagtcttt gttggattcg 120
agtaggctca ggatctgctg aaggctcgag gagttagtcc ccgcaatcaa gagcctgtct 180
tcctgaagcc cttggtgata ttttgccact cagccaagaa tgaggatgca tccttcagat 240
tctctatgtc ccgaacctgg aacccatcca cgccagcttg cagccaaaac tccagagcat 300
ccttcacctt ggtggaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 352

```

<210> 419

<211> 344

<212> DNA

<213> Homo sapiens

<400> 419

```

ctggacacca taatcccttt taagtggctg gatggtcaca cctctcccat tgacaagctg 60
ggttaagtca ataggttgac taggatcaac acgacccaaa tcaataagat actgcagtct 120
attgagactc aaaggcttat actggcgtct gaaactatgt ccttcgttaa acccgatttt 180
tggaattcgg atgtaaaatg gagtctggcc tccctcaaag cccaagcggg gccgggttcc 240
tctttgcctt tctcctttat ggcctctgcc acattttcta cctcttctcc gacctcttgg 300
tcttctctcc ggtttcttgg agccgggatt cggctttaag ttgg 344

```

<210> 420

<211> 935

<212> DNA

<213> Homo sapiens

<400> 420

```

cgaaagtcaa cgtaagggg ctcaggtgaa ccatgatgat gaccttctgt tgactttgaa 60
atattggctc ttgtgggtga caaaagccag acaagctgtg gctgtggtcc gattttaaga 120
cgaggttctc aaagatccaa aggagggaag gggtattgga aacactgtgt atcatctgag 180
acacacgtgt cctcatgatc ttaaatgcct actttaaaagc cacctaatac tgcccttcac 240
tgtgtgcaga agagatttct acaaaagcac tcagaattct ggaggcagtt gtgattttgc 300
catgtggcag ttggttttgg gagttgggca ggtgtgaaag ggtaaaactc cacttctgaa 360
tgctgcttct gccccctggg acccagcaca ttgttagacc atcttcttga ctgaaaattc 420
tctcctgatg ctgagccctg caccaccacc ttctttttcc taactatgaa ttgatggcaa 480
agtccactca aaacaaccag ttaagtgtc acgagagagt agtcaagcac ctccagaaag 540
aaaccgggtt tttgttcaca tagcaggaag tgactccctg ggtggttaatt tatcttgaa 600
acacaggtag attggcagaa aaacgggaac atgtaggtag cgcgatgttg gtgcatgtcc 660
attacttttg gataggcttt ctacgtcttt cctcaaatga tagttgagcc agttttccag 720
tggaatttct gagtgacttg cgcttgtctt atggtgtggt caagggacgt tcagaactac 780
ggaaaacttt tactgaaaca gcgaagcaga gtataccggc atgagaggga agatgaacac 840
tcacctatgt accactcttt gacaataaat atagtatttc tcaaaaaaaaa aaaaaaaaaa 900
agtaaaaaaa ctgaaatcgc aagtcaaaaa atcca 935

```

<210> 421

<211> 745

<212> DNA

<213> Homo sapiens

<400> 421

```

ggcttcgagc ggccgcccgg gcaggtccta gatgtcattt gggacccttc acaaccattt 60
tgaagccctg tttgagtcctc tgggatattg gagctgtttc tatgcataat ggatattcgg 120
ggttaacaac agtcccctgc ttggcttcta ttctgaatcc ttttctttca ccatggggtg 180
cctgaagggt gctgatgca tatgttaca tgccaccag tgtaaaagcag ctacaattag 240
gagtggaagt gttctgtagc atcctattta aataagccta ttttatcctt tggcccgta 300
actctgttat ctgctgcttg tactgtgccc tgactctcat tgaccatatt 360
ccacgacctt ggttgtcatc cattacttga tcctacttta catgtctagt ctgtgtggtt 420
gggtgtgaat aggccttctt ttacatgggt ctgccagccc agctaattaa tgggtgcacgt 480
ggacttttag caagcgggct cactggaaga gactgaacct ggcatggaat tcctgaagat 540
gtttgggggt tttttcttct ttaatcgaaa gttaacattg tctgaaaagt tttgttagaa 600
ctactgcgga acctcaaaat cagtagattt ggaagtgatt caaagctaaa ctttttctct 660
ggccctcctt gtgttctaag tgcttgcaag tgaatacta ggatgtccaa gatgccagtt 720
tttgccttct tgtagttgt cagac 745

```

<210> 422
 <211> 764
 <212> DNA
 <213> Homo sapiens

<400> 422
 gagttcagta gcaaagtcac acctgtccaa ttccctgagc ttgctcact cagctaattgg 60
 gatggcaaaag gtggtggtgc tttcatcttc aggcagaagc ctctgcccac cccctcaag 120
 ggctgcaggc ccagttctca tgctgccctt ggggtggcat ctgttaacag aggagaacgt 180
 ctgggtggcg gcagcagctt tgctctgagt gcctacaaag ctaatgcttg gtgctagaaa 240
 catcatcatt attaaacttc agaaaagcag cagccatggt cagtcaggct catgctgcct 300
 cactgcttaa gtgcctgcag gagccgcctg ccaagctccc cttcctacac ctggcacact 360
 ggggtctgca caaggctttg tcaaccaaag acagcttccc ccttttgatt gcctgtagac 420
 tttggagcca agaaacactc tgtgtgactc tacacacact tcagggtggt tgtgcttcaa 480
 agtcattgat gcaacttgaa aggaacagc ttaatggtgg aaatgaacta ccatttataa 540
 cttctgtttt ttatttgaga aaatgattca cgaattccaa atcagattgc caggaagaaa 600
 taggacgtga cggtagctgg ccctgtgatt ctcccagccc ttgcagtccg ctagggtgaga 660
 ggaaaagctc ttactttccg cccctggcag ggaacttctg gttatgggag aaaccagaga 720
 tgggaatgag gaaaatatga actacagcag aagcccctgg gcag 764

<210> 423
 <211> 1041
 <212> DNA
 <213> Homo sapiens

<400> 423
 ctacagagagg ttgaaagatt tgccctacgaa agggacagt atgaagctaa gctctagatc 60
 caggatgtct gacttcaaat tgaaaactccc aaagtaatga gtttggaagg gtgggtgtg 120
 gcctttccag gatgggggtc ttttctgctc ccagcggata gtgaaacccc tgtctgcacc 180
 tgggtgggag tggtgctttc ccaaaggttt tttttttagg tccgtcgctg tctgtggat 240
 taggcattat tatctttact ttgtctccaa ataacctgga gaatggagag agtagtgacc 300
 agctcagggc cacagtgcga tgaggaccat cttctcacct ctctaaatgc aggaagaaac 360
 gcagagtaac gtggaagtgg tccacaccta ccgccagcac attgtgaatg acatgaaccc 420
 cggcaacctg cacctgttca tcaatgccta caacaggat tgggatgtag ttcagccaca 480
 tcattgctat ttatgaggtg tcttctgtag atccgaaatg tgggacagat gagagggaga 540
 gtataaaatg agcgggaagag gcaggtctct agtttgagca aatagattaa taggacaggt 600
 gtccccagga aggacacctg gcctgtaagc tggttcctgg cattcagctc gccttgacag 660
 gatctgaaca aacactccag accactgggg gtgcagacgt gagagggacg cagtcgcaca 720
 ctacagagggt tgagagtaaa tatgtgtgcc cgctgctgac cttcacgaaa ggccaaatgt 780
 aagaagagct aagtggagaga gcagcaaagc actcctggag gccggggata atccaggcag 840
 gcttctggga gtttgtcatt ccaaggataa ggaggacctg aacatggcct ttgcctaagg 900
 cgtggccctc tcaaccagca ctagggtgct atctggagct cagctagggg aggagacagc 960
 tcagggccat tgggtgtcagc cagagactct gtaatcttcc agggagctcg ctcaacctgc 1020
 tgagctcgct ctgccacgca c 1041

<210> 424
 <211> 1288
 <212> DNA
 <213> Homo sapiens

<400> 424
 ctaagaactg agacttgtga cacaaggcca acgacctaa attagcccag gttgtagct 60
 ggaagacctc caacccaagg atggaaggcc cctgtcacia agcctacctc gatggataga 120
 ggacccaagc gaaaaaggtc tctcaagact aacggccgga atctggaggc ccatgaccca 180
 gaacccagga agtagagaag cttgaagacc tggggaaatc ccaagatgag aaccctaaa 240
 cctacctctt ttctattgtt tacacttctt actcttagat atttccagtt ctctgttta 300
 tctttaagcc tgattctttt gagatgtact ttttgatgtt gccggttacc tttagattga 360
 cagtattatg cctgggcccag tcttgagcca gctttaaatc acagctttta cctatttgtt 420
 aggctatagt gttttgtaaa cttctgtttt tattcacatc ttctccactt gagagagaca 480
 ccaaaatcca gtcagtatct aatctggctt ttgttaactt ccctcaggag cagacattca 540
 tataggtgat actgtatttc agtcttttct tttgacccca gaagccctag actgagaaga 600

111

```

taaaatggtc aggttgttgg ggaaaaaaaaa gtgccaggct ctctagagaa aaatgtgaag 660
agatgctcca ggccaatgag aagaattaga caagaaatac acagatgtgc cagacttctg 720
agaagcacct gccagcaaca gcttccttct ttgagcttag tccatccctc atgaaaaatg 780
actgaccact gctgggcagc aggagggatg atgaccaact aattcccaaa cccagtcctc 840
attggtacca gccttgggga accacctaca cttgagccac aattggtttt gaagtgcatt 900
tacaagtttc tggcatcact accactactg attaaacaag aataagagaa cattttatca 960
tcatctgctt tattcacata aatgaagtgt tgatgaataa atctgctttt atgcagacac 1020
aaggaattaa gtggcttctg cattgtcctt ctacctcaa gataatttat tccaaaagct 1080
aagataaatg gaagactctt gaacttgtga actgatgtga aatgcagaat ctcttttgag 1140
tctttgctgt ttggaagatt gaaaaatatt gttcagcatg ggtgaccacc agaaagtaat 1200
cttaagccat ctgatgtca caattgaaac aaactgggga gttggttgct attgtaaaat 1260
aaaatatact gttttgaaaa aaaaaaac                                     1288

```

<210> 425
 <211> 446
 <212> DNA
 <213> Homo sapiens

```

<400> 425
ccacttaaaag ggtgcctctg ccaactgggtg gaatcatcgc cacttccagc accacgccaa 60
gcctaacatc ttccacaagg atcccgatgt gaacatgctg cacgtgtttg ttctgggcga 120
atggcagccc atcgagtacg gcaagaagaa gctgaaatac ctgccctaca atcaccagca 180
cgaatacttc ttcttgattg ggccgcgcgt gctcatcccc atgtatttcc agtaccagat 240
catcatgacc atgactgtcc ataagaactg ggtggacctg gcctgggccc tcagctacta 300
catccggttc ttcatcacct acatcccttt ctacggcatc ctgggagccc tccttttctc 360
caacttcacg aggttctctg agagccactg gtttgtgtgg gtcacacaga tgaatcacat 420
cgtcatggag attgaccagg aggacc                                     446

```

<210> 426
 <211> 874
 <212> DNA
 <213> Homo sapiens

```

<400> 426
tttttttttt tttttttta taaagatttg atttattcaa gtatgtgaaa 60
acattctaca atggaaaactt ttattaaatg ctgcatgtac tgtgctatgg accacgcaca 120
tacagccatg ctgtttcaga agacttgaaa tgccattgat agtttaaaaa ctctacaccc 180
gatggagaat cgaggaagac aatttaatgt ttcactctga tccagagggtg catcaaatta 240
aatgacagct ccacttggca aataatagct gttacttgat ggtatccaag aagaaatggt 300
tgggtgatgga taaattcaga aatgcttccc caaagggtggg tgggtttttaa aaagttttca 360
ggtcacaacc cttgcagaaa acactgatgc ccaacacact gattcgcggg ccaggaaaaca 420
cgggtcttcc aagttccaag gggctggggg tccccaacga tcaagttcct gtgctgtaat 480
caagagggtc ctttgactg gatagggagc acttgggagc tgtacaccat cagtcataat 540
ggatggcagt gtaaaagatg atccaaatga cctgagatgc tcctgaggag tgggtgcacca 600
gacccaggag tgccactgta gggctgcttc tttgctttag tcatcacaca cacacacagc 660
tccagagcag caatggcctt tcctgtaaca ggaaaaaagc ctctgctat tcccaagaac 720
cctcgtaatg gcaaaactcc ccaaagaca cccaggacca cagcaatgat ctgtcggaac 780
cagtagatca catctaaaaa ttcatcctta tcctcccagg ccgcgtcgct ccgcagcacc 840
ttactccaga cggagacttt gagggccccg ttgg                                     874

```

<210> 427
 <211> 638
 <212> DNA
 <213> Homo sapiens

```

<400> 427
acttgtaatt agcacttggt gaaagctgga aggaagataa ataacactaa actatgctat 60
ttgatttttc ttcttgaaag agtaagggtt acctgttaca ttttcaagtt aattcatgta 120
aaaaatgata gtgattttga tgtaatttat ctcttggttg aatctgtcat tcaaaaggcca 180
ataatttaag ttgctatcag ctgatattag tagctttgca accctgatag agtaaaataa 240
ttttatgggc ggggtgccaaa tactgctgtg aatctatttg tatagtatcc atgaatgaat 300

```


112

```

ttatggaaat agatatttgt gcagctcaat ttatgcagag attaaatgac atcataatac 360
tggatgaaaa cttgcataga attctgatta aatagtggtg ctgtttcaca tgtgcagttt 420
gaagtattta aataaccact ctttcacag tttattttct tctcaagcgt tttcaagatc 480
tagcatgtgg attttaaaag atttgccctc attaacaaga ataacattta aaggagattg 540
tttcaaaata tttttgcaaa ttgagataag gacagaaaga ttgagaaaca ttgtatatatt 600
tgcaaaaaca agatgtttgt agctgtttca gagagagt 638

```

<210> 428

<211> 535

<212> DNA

<213> Homo sapiens

<400> 428

```

acaagatgat tcttctcct caatttgaca gatcaaagaa gtatcccttg ctaattcaag 60
tgtatgggtg tccctgcagt cagagtgtaa ggtctgtatt tgctgttaat tggatatctt 120
atcttgcaag taagggaagg atgggtcattg ccttggtgga tggtcgagga acagctttcc 180
aagggtgacaa actcctctat gcagtgtatc gaaagctggg tgtttatgaa gttgaagacc 240
agattacagc tgtcagaaaa ttcatagaaa tgggtttcat tgatgaaaaa agaatagcc 300
tatggggctg gtcctatgga ggatacgttt catcactggc ccttgcatct ggaactggtc 360
ttttcaaatg ttgtatagca gtggctccag tctccagctg ggaatattac gcgtctgtct 420
acacagagag attcatgggt ctccaacaa aggatgataa tcttgagcac tataagaatt 480
caactgtgat ggcaagagca gaatatttca gaaatgtaga ctatcttctc atcca 535

```

<210> 429

<211> 675

<212> DNA

<213> Homo sapiens

<400> 429

```

actattttca accctgagca ttaacactgc ataccaaggg ggggtgggtc aagaagctgg 60
ttagatcgaa gcacaagcac aagccactga tattctctat gtgatcaggt ttttcaaaa 120
aaatacatag ttttcaataa ataatgctta attttacaac ttgatacag caatgtcata 180
caccgtttca acacactaca ctctgcatgc tagatagtct acgagaagac gaaactttgc 240
catgcatttt ctttccccc tagtgctatc aaacacttca tctccagcg cactgcctca 300
ggtagcttta cttctctct gtttcacagc aataggccgt gcgctggcat gcaaactcta 360
aaaaaggtcc ccccaacaaa ccactcagac ttctacacaa aagggttttt cagcttttct 420
gctcccaaac ctggagtggc taagaaagta agtttcatgt ggccttgga aatacacact 480
tggttaacagt gtcatgctga aaactgctct aaaacatcag gtggttctgt cctggtggcc 540
gtcacgaagc attatgggat gccataacca ctaggagtcc caaaccgga aaaaaggcc 600
tccgttttaa aacagtcaat tcaaaaaagg tgtcacagaa caaatgcaaa agactcttaa 660
accacaaca tatgt 675

```

<210> 430

<211> 434

<212> DNA

<213> Homo sapiens

<400> 430

```

acctctgcca gaagtccagc gagaggacct cacagtagag cacaggccac tccgggagtg 60
catcagaaga ttcatcctca tggaggaaga aggcttcaaa cgtgaatggg taggagaagt 120
gagccacctt gtccattgcc agggacttgg tggtcaggt ctgtgttact cctgagagct 180
gctggaatgc tgggcttgac cagtgcagc ttggcaattc tacaaagaag tggacgtaga 240
gattgtcata ctcatagcct tgggctgaaa cgacctctcc atttacaag agccggaggg 300
cacctgggac agtcatctca aagtcggtgc ctacgaggct gctgagatac tccttggtgc 360
ggccataaag atccttgaac actcgccgtt cccgctcctc ctctccggc tgtgcgtggg 420
gggaaacatt gtcg 434

```

<210> 431

<211> 581

<212> DNA

<213> Homo sapiens

<400> 431
 acacaagcct ccagcccgac ccagcggcct aatgaaactc tggcaaccta tcctgggctg 60
 ggccacgagt atccagctcc aagcccaagt gaggcgggga gtcaacttcc ccatgattgc 120
 caagtgacca agaccagaag cagggacgat taggctagtt ctgcccgaag gtgaactgga 180
 gaccctgtct ctgcccctct tccctggcct gtcccacaga catcccgttg ttttaaccac 240
 tgcccttgca aggacctgct ctgtccactc caaatcaaag gatacttgca tccttcttac 300
 acagactccc atctctctgc tcatagtggc cccaggctgc ccgagaaaaa gaaacttggg 360
 tcagtagaag gctcattagt gtgaaggagt gagaggccag gccttcctgt gacataatgc 420
 ttctatgctt gtttcctaaa cacttggctc acacacaata cctgggcagg aagagagaac 480
 caagcaccac tggatggctc tggagccagg ggacttctat gcacatacaa ccaacatcac 540
 cccactctgc tcatctgtgc ctccaccctg aacagcagag t 581

<210> 432
 <211> 532
 <212> DNA
 <213> Homo sapiens

<400> 432
 actccaactc aagtttacaa gttacacctt tgccacagcc ttggctaaat cttgaactag 60
 tgcagaattc agctgtggta gagtgctgat cttagcatgc ttgatgtgg catacttggt 120
 cttgacagtc atgtgctttg taagtccttg atttaccatg actacattct tagccagggtg 180
 ctgcataact ggaagaagag attcttcagt atatgacagg taatgttgta gagttgggtg 240
 ccattcacca ttatccagaa ttttcagtgc taagcaaaaa gtcctgtctg caatttgaga 300
 aggaggaaag tgcaccatgt catagtccaa catagttagt tccatcaggt atttggccaa 360
 agtatgttgc tcgacatcaa cctctccaat cttagatgct ctccgaagga agtgcaagg 420
 tagaggccga cccagaccaa agtttaaagc tcttagaatc ttcatttcca tctgtctgat 480
 ttggtgctta gtataagtggt tgtcagtcac aaaagcaaa gtcaccaattt ct 532

<210> 433
 <211> 531
 <212> DNA
 <213> Homo sapiens

<400> 433
 acttggtttt acagctcctt tgaaaactct gtgtttggaa tatctctaaa aacatagaaa 60
 acactacagt ggtttagaaa ttactaattt tacttctaag tcattcataa accttgctta 120
 tgaaatgact tcttaaatat ttagttgata gactgctaca ggtaataggg acttagcaag 180
 ctcttttata tgctaaagga gcatctatca gattaagtta gaacatttgc tgtcagccac 240
 atattgagat gacactagggt gcaatagcag ggatagattt tgttgggtgag tagtctcatg 300
 ccttgagatc tgtggtggtc ttcaaaatgg tggccagcca gatcaaggat gtagtatctc 360
 atagtcccca ggtgatattt ttcttattag aaaaatatta taactcattt gttgtttgac 420
 acttatagat tgaaatttcc taattttatt taaattttaa gtggttcttt gggtccagtg 480
 ctttatgttg ttgttggttt tggatggtgt tacatattat atgttctaga a 531

<210> 434
 <211> 530
 <212> DNA
 <213> Homo sapiens

<400> 434
 acaagagaaa acccctaaaa aaaggatggc ttttagatgac aagctctacc agagagactt 60
 agaagttgca ctagctttat cagtgaagga acttccaaca gtcaccacta atgtgcagaa 120
 ctctcaagat aaaagcattg aaaaacatgg cagtagtaaa atagaaacaa tgaataagtc 180
 tctcatatc tctaattgca gtgtagccag tgattattta gatttggata agattactgt 240
 ggaagatgat gttggtggtg ttcaaggga aagaaaagca gcatctaaag ctgcagcaca 300
 gcagaggaag attcttctgg aaggcagtga tggatgagtg gctaatagaca ctgaaccaga 360
 ctttgcacct ggtgaagatt ctgaggatga ttctgatttt tgtgagagtg aggataatga 420
 cgaagacttc tctatgagaa aaagtaaaat taaagaaatt aaaaagaaag aagtgaagg 480
 aaaatcccca gtagaaaaga aagagaagaa atctaaatcc aaatgtaatg 530

<210> 435
 <211> 677

<212> DNA

<213> Homo sapiens

<400> 435

```

accttatgat ctaattaata gatattagaa acagtagaaa gacaagttac acgtcaatgc 60
ccaatgacta gagtcaacat taaagagttg taatttaagt aatccaaact gacatctaata 120
tccaaaatca tttataaaaat gtatttggct ttggaatcca caggacttca aacaagcaaa 180
gtttcactgc agatagtcac aaagatgcag atacactgaa atacttaaga gccttattaa 240
tgatttttgt tatattggat cttctgtttt tttcttatta tgggccgaag cctccttaata 300
accaatttat cagacagaag catgtcatct tgttgttcaa gataatccag taaattttca 360
gtccattcaa gtgccgcttt atggctaata cgcttctctg gattcagttc tgtttttcta 420
ctcttactgg aaggcttttg ctcagcagcc ttggtctggt cctcagcact ttcactgtca 480
gtcagacact gacagcttga gtcactgtct cgagagtcga accactgac aatattctca 540
atgtcaacat gttcacattc ttctgtgttc tgtaaaactg ttgctaaatt agctgctaaa 600
atggctcctt catcaatggt catacctgaa ttctcttcat tgccaggga aagttttttc 660
catgctttgg ttatggt

```

677

<210> 436

<211> 573

<212> DNA

<213> Homo sapiens

<400> 436

```

acctcttagg gtgggagaaa tgggtgaagag ttgttctac aacttgctaa cctagtggac 60
agggtagtag attagcatca tccggataga tgtgaagagg acggctgttt ggataataat 120
taaggataaa atttggccag ttgacagatt ctgtttccag cagtttttac agcaacagtg 180
gagtgcttca gtattgtgtt cctgtaaatt taattttgat ccgcaatcat ttggtatata 240
atgctgtttg aagttttgtc ctattggaaa agtcttgtgt tgcagggtg cagttaagat 300
ctttgtgatg aggaatggga tgggctaatt ttttgccgtt ttcttggaa tgggggcatg 360
gcaaatacag tagggtagtt tagttcttta cacagaacat gataaactac acctgttgat 420
gtcaccgtct gtcaatgaat attatagaag gtatgaaggt gtaattacca taataacaaa 480
acaccctgtc tttagggtg acctttcgtc ctttgacctc ctcagcctcc attccatct 540
tcgctcagac tgcaagtatg tttgtattaa tgt

```

573

<210> 437

<211> 645

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(645)

<223> n = A,T,C or G

<400> 437

```

acaattggtt tccatatctt gttgaaattg taatgggaaa acaatatatt tcaatctcta 60
tgtagatagt gggtttttgt tttcataata tattctttta gtttactgta tgagttttgc 120
aggactgcat aatagatcac cacaatcata acatcttagg accacagaca tttatgagat 180
catggcttct gtgggttaga agtatgctca tgtcttaact gggtcctctg ctgagtctta 240
tctggctgca atcaaggtgt cagctgggct gaattttcat ttggaatctt gactgggaaa 300
gagtcgtgctt ccaaggtcat gaagtttgct ggcaaaatgt atgtttttat gacagtatga 360
ctgaaatccc aagctatctc ctgactttta gctgggtaat ctcaggccct aaatgttgcc 420
tacagttcct agagctggt cagagtctct agccatgtgg atttcctcaa catggctgct 480
tgcttcatca agtcagcaag aatagcctgt catatcagtg tatatcaggc tcaactcagga 540
taatttcctt actgatgagc caaacactaa ctgattttag agcttaacta catctgcaaa 600
attcngttca ccagaggcaa gtcatatcca ggaaggaga agtgt

```

645

<210> 438

<211> 485

<212> DNA

<213> Homo sapiens

```

<400> 438
acagaattga gagacaagat tgcttgtaat ggagatgctt ctagctctca gataatacat 60
atctctgatg aaaatgaagg aaaagaaatg tgtgttctgc gaatgactcg agctagacgt 120
tcccaggtag aacagcagca gctcatcact gttgaaaagg ctttggcaat tctttctcag 180
cctacaccct cacttgttgt ggatcatgag cgattaaaaa atcttttgaa gactgttggt 240
aaaaaagtc aaaactacaa catatttcag ttgaaaaatt tgtatgcagt aatcagccaa 300
tgtatttatc ggcatcgcaa ggaccatgat aaaacatcac ttattcagaa aatggagcaa 360
gaggtagaaa acttcagttg ttccagatga tgatgtcatg gtatcgagta ttctttatat 420
tcagttccta ttttaagtcat ttttgtcatg tccgcctaata tgatgtagta tgaaaccctg 480
catct 485

```

```

<210> 439
<211> 533
<212> DNA
<213> Homo sapiens

```

```

<400> 439
acagcagttt cctcatccct gcagctgtgt ttgaacaggt catttaccat actgtcctcc 60
aggttcaaca gtatggctcc aaatgatgaa atttcattct gattttctgg ctgaagacta 120
ttctgtttgt gtatgtccac cacagttact ttatcccttc atctgtggat gggcagaatg 180
aaacatatat ggaaatgttc tgtgcaataa aaacagcagt ggtaacacag atgtaggctc 240
tgagtgtctc actggagact gaagtccaca gatatgcaac aaagcctttg tctocctgat 300
gtttttgcct cctgctggtc atgtgctttc acacatcaag agaggacatt taacatttga 360
gccacagtgt catttgctgt tgtctgatgg ttggttgcca gagaatttga actggagatg 420
aactttatta tccaggacgc tgagagtata acatgcatga cagagctttt agagcactgt 480
gatgtaacat gtcaagcaga aatagggagc atgtttacag ccattctatg aaa 533

```

```

<210> 440
<211> 341
<212> DNA
<213> Homo sapiens

```

```

<400> 440
catggggtag ggggggtcggg gattcattga attgtggttg gcaggagcaa gccctgctca 60
cactctcaca ctgcgaccca gaattgtcaa agatacagat tgtaaaaatc tacgatccct 120
cagctctcact cacaaaaaat aaaatctcat gtccccaacg aaccagaggt cagacgacag 180
ctggagcatt ggccagggaca gtcagaaagg agacaagtga aaacggtcag atggacacag 240
gcggaggaga aaagacagag ggagagagac catcggaac aatcagaggg gccgagacga 300
tcagaaaagg gtcagcccga gacaggctga gccagagttt c 341

```

```

<210> 441
<211> 572
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(572)
<223> n = A,T,C or G

```

```

<400> 441
aagtttgggg ataatttatt atgcagcaag agataatata caggacttct canagcactt 60
aatatgttaa tataaatctc caanaaaaaa gatatacaat gaaacattcc tcttagttat 120
ctggccaagg anactttntt tttttganaa tattcttcaa aaagctgac taatgatatg 180
gctctggtcc tacaattcca tgtaacttct aaccttgatt ttatctcat agcaaatcat 240
ttatccttcc agaacctcaa cttttccctt ttacaaagta gaaataaacc atctgccttt 300
acataaatca ttaatacagc cctggatggg cagattctga gctatttttg gctggggggt 360
gggaaatagc ctgtggaggt cctaaaaaga tctacggggc tcgagatggt tctctgcaag 420
gtagcaggtg ggctcagggc ccatttcagt ctttgttccc caggccattt ccacaaaatg 480
gtgagaaaata gtgtcttctt ttagcttgct cataactcaa agatgggggg catggacctg 540
ggcctttcta ggctagggca tgaacctcct cc 572

```

116

<210> 442
 <211> 379
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(379)
 <223> n = A,T,C or G

<400> 442
 tcccagctgc actgcttaca cgtcttcctt cgtnttcacc taccocgagg ctgactcctt 60
 ccccagntgt gcagctgccc accgcaaggg cagcagcagc aatgagcctt cctctgactc 120
 gctcagctca cccacgctgc tggccctgtg agggggcagg gaaggggagg cagccggcac 180
 ccacaagtgc cactgcccga gctggtgcat tacagagagg agaaacacat cttccctaga 240
 gggttcctgt agacctaggg aggaccttat ctgtgcgtga aacacaccag gctgtgggccc 300
 tcaaggactt gaaagcatcc atgtgtggac tcaagtcctt acctcttccg gagatgtagc 360
 aaaacgcatg gagtgtgta 379

<210> 443
 <211> 511
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(511)
 <223> n = A,T,C or G

<400> 443
 acatgcccc aaaggtcgc ttcattgcta cgattctcta cttaaatacca cattcacagc 60
 tattgcctca gaccctctgg aggaggggccc aggggttagc tggctttgaa tagcatgtag 120
 agcacaggca gtgtggccac aaatgtcaca caggtgacca ggggtgctata gatggtgttc 180
 ctgttgactt gggcttctag tctctgctcc gtgtctgaca gtgccaagat catgctcccc 240
 tgctccagca agaagctggg catagccccg tctgtctggt ccaccaggcc tgggtgtgct 300
 gcagacttta caagctgaac caccagagcc atttggttac aagtcttttc taggcatca 360
 agtgcctctc gtaagccttc tagacatgaa tggacttgcc tggaaatgact aagctgctct 420
 ttcaaggcag ctgaaaggac atcnacatct ctgtctctgg tcgggggact acctgcctgt 480
 gaccagagt cctgccctgg cccagcagca t 511

<210> 444
 <211> 612
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(612)
 <223> n = A,T,C or G

<400> 444
 acaggaagaa ttctacagtt aatctatcac agtgttccag caaagcatat gttgaaaact 60
 acagttttca atctaaccatc taaattttta aaagtagcat ttcagcaaca aacaagctca 120
 gagaggctca tggcaaaagt gaaataacag aactattgct cagatgtctg caaagtcaag 180
 ctgctgcctc cagctccgcc cacttgaagg cttaggcaga cacgtaagggt ggcggtggct 240
 ccttggcagc accattcaca gtggcatcat catagcgagg tagcagcacc gtagtgtcat 300
 tgctggtaac ataaaccagg acatcagagg agttcctacc attgatgtat cggtagcagt 360
 tccaaacaca gctaatacaag taacccttaa aagtcaagat aatgctaata aacagaagaa 420
 taataaggac caaacaggta ggattcactg acatgacatc atctctgtag ggaaaattag 480
 gaggcagttg ccgtatgtat tcctgaatgg agtttgata aataagcaca gtgattgcaa 540
 ccaacantct cagggcaaaag tcaaagatct ggtaacagaa gaatgggatg atccaggctg 600
 cgcgttgctt gt 612

117

<210> 445
<211> 708
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(708)
<223> n = A,T,C or G

<400> 445
accatcctgt tccaacagag ccattgccta ttcctaaatt gaatctgact ggggtgtgccc 60
ctcctcggaa cacaacagta gaccttaata gtggaaacat cgaatgtgcct cccaacatga 120
caagctgggc cagctttcat aatgggtgtg ctgctggcct gaagatagct cctgcctccc 180
agatcgactc agcttggatt gtttacaata agcccaagca tgctgagttg gccaatgagt 240
atgctggcct tctcatggct ctgggtttga atgggcacct taccaagctg gcgactctca 300
atatccatga ctacttgacc aagggccatg aaatgacaag cattggactg ctacttgggtg 360
tttctgctgc aaaactaggc accatggata tgtctattac tcggcttgtt agcattcgca 420
ttcctgctct cttaccccca acgtccacag agttggatgt tcctcacaat gtccaagtgg 480
ctgcagtggg tggcattggc cttgtatatc aaggacagc tcacagacat actgcagaag 540
tcctgttggc tgagatagga cggcctcctg gtccctgaaat ggaatactgc actgacagag 600
agtcatactc cttagctgct ggcttggccc tgggcatggt ctncctgggg catggcagca 660
atttgatagg tatgtntgat ctcaatgtgc ctgagcagct ctatcagt 708

<210> 446
<211> 612
<212> DNA
<213> Homo sapiens

<400> 446
acaagcaacg cgcagcctgg atcatcccat tcttctgtta ccagatcttt gactttgccc 60
tgaacatggt gggtgcaatc actgtgctta tttatccaaa ctccattcag gaatacatac 120
ggcaactgcc tctaattttt ccctacagag atgatgtcat gtcagtgaat cctacctgtt 180
tggctcctat tattcttctg tttattagca ttatcttgac ttttaagggg tacttgatta 240
gctgtgtttg gaactgctac cgatacatca atggtaggaa ctccctctgat gtccctggtt 300
atgtttaccg caatgacact acggtgctgc taccctcgta tgatgatgcc actgtgaatg 360
gtgctgcaa ggagccaccg ccaccttacg tgtctgccta agccttcaag tgggcggagc 420
tgagggcagc agcttgactt tgcagacatc tgagcaatag ttctgttatt tcacttttgc 480
catgagcctc tctgagcttg tttgttgctg aaatgctact ttttaaaatt tagatgttag 540
attgaaaact gtatgtttca acatatgctt tgcgtggaaca ctgtgataga ttaactgtag 600
aattcttctc gt 612

<210> 447
<211> 642
<212> DNA
<213> Homo sapiens

<400> 447
actgaaagaa ttaaagtcag aagtcttccc aaaacaaaaa gaactgccc aagagaaaaat 60
cctttctgat acttttcatt gctaaaataa aacaggcggg aaatgtggaa aagaaattca 120
acaaaataat gtagcaccag aagaacaagt cctagatgat tcaagttcaa aaggtaagct 180
ccagcaatgt ggaagaggta aagaccaatg tagacaagct gacgaggaat atcttctttt 240
ttgggttttct ggaagtagag ttcaggaaaa gcatgaagcc agtaagccag ctgtgatatg 300
tagaaaaact tcatattgaa tgtcatcagg ttatggggat aagccctcca taagatagtt 360
gggtctgaga tgtagttttc agagatgaga atgaatgtgc cccaaacaca ggcaaaaagg 420
tagaacgcac taagctgacc agattcatta aacttgctgt gttttgtttt ggagaagtgc 480
attcgctgt taattttatc caacatatac tcttgaatta cggcatgaat aattatcgcc 540
actagcatgt agaagaaaac agtagccaaa tctttgatgc catagtaata aagggacact 600
gattcagtag cttgttcttc tgttgcctgg aggggtgacat tg 642

<210> 448

118

<211> 394
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(394)
<223> n = A,T,C or G

<400> 448
accagaagac cttagaaaaa ggaggaaagg aggagaggca gataatttgg atgaattcct 60
caaagngttt gaaaatccag aggttcctag agaggaccag caacagcagc atcagcagcg 120
tgatgttatc gatgagccca ttattgaaga gccaaagccg ctccaggagt cagtgatgga 180
ggccagcaga acaaacatag atgagtcagc tatgcctcca ccaccacctc agggagttaa 240
gcgaaaagct ggacaaattg acccagagcc tgtgatgcct cctcagcagg tagagcagat 300
ggaaatacca cctgtagagc ttccccaga agaacctcca aatatctgtc agctaatacc 360
agagtttagaa cttctgccag aaaaagagaa ggag 394

<210> 449
<211> 494
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

<400> 449
acaaaaaaca caaggaatac aaccaatag aaaatagtcc tgggaatgtg gtcagaagca 60
aaggcntgag tgtctttctc aaccgtgcaa aagccgtgtt cttcccgga aaccaggaaa 120
aggatccgct actcaaaaac caagaattta aaggagtttc tttaaatttcg accttgtttc 180
tgaagctcac ttttcagtgc cattgatgtg agatgtgctg gagtggctat taacctttt 240
ttcctaaaga ttattgttaa atagatattg tggtttgggg aagttgaatt ttttataggt 300
taaagtcat tttagagatg gggagaggga ttatactgca ggcagcttca gccatgttgt 360
gaaactgata aaagcaactt agcaaggctt cttttcatta ttttttatgt ttcacttata 420
aagtcttagg taactagtag gatagaaaca ctgtgtcccg agagtaagga gagaagctac 480
tattgattag agcc 494

<210> 450
<211> 547
<212> DNA
<213> Homo sapiens

<400> 450
actttgggct ccagacttca ctgtccttag gcattgaaac catcacctgg tttgcattct 60
tcatgactga ggttaactta aaacaaaaat ggtaggaaag ctttcctatg cttcgggtaa 120
gagacaaatt tgcttttgta gaattggtgg ctgagaaagg cagacagggc ctgattaaag 180
aagacatttg tcaccactag ccaccaagtt aagttgtgga acccaaagg gacggccatg 240
gaaacgtaga tcatcagctc tgctaagtag ttaggggaag aaacatatc aaaccagtct 300
ccaaatggga tcctgtggtt acagtgaatg gccactcctg ctttattttt cctgagattg 360
ccgagaataa catggcactt atactgatgg gcagatgacc agatgaacat catcatccca 420
agaatatgga accaccgtgc ttgcatcaat agatttttcc ctgttatgta ggcattcctg 480
ccatccattg gcaattggct cagcacagtt aggccaaaca ggacataata gacaagtcca 540
aaacagt 547

<210> 451
<211> 384
<212> DNA
<213> Homo sapiens

<220>

119

<221> misc_feature
 <222> (1)...(384)
 <223> n = A,T,C or G

<400> 451
 actacttntt gggttaaaang ccactggtag agtcatctga ntgtaaacia tgtccctgca 60
 ctgctggaaa aatccactgg ctccaagaa aagaaaatgg tctgaagcct ctgttgtggc 120
 tctcacaact catctttccc taagtcacat agctccacat cactgaggtc aatgtcatcc 180
 tccacgggaa gctcgccatc cctgccgtcc caaggctctc tctcaacgat ggtagggaaa 240
 gccccgcctc ctacaggtgc cgtggagcca cgcccaaaag agagctccct gagaaactcg 300
 ttgatgcctt gctcactgaa ggagcctttt agcagagcaa atttcatctt gcgtgcattg 360
 atggcgccca tggcggggta ccca 384

<210> 452
 <211> 381
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(381)
 <223> n = A,T,C or G

<400> 452
 actctaaagt tgccactctc acaggggtca gtgataccca ctgaacctgg caggaacagt 60
 cctgcagcca gaatctgcaa gcagcgctg tatgcaacgt ttagggccaa aggctgtctg 120
 gtgggggtgt tcatcacagc ataatggcct agtaggtcaa ggatccaggg tgtgaggggc 180
 tcaaagccag gaaaacgaat cctcaagtcc ttcagtagtc tgatgagAAC tttactgtg 240
 gactgagaag cattttcctc gaaccagcgg gcagtgcgga tggctgctaa ngcactctgc 300
 aatactttga tatccaaatg gagttctgga tccagttttc naagattggg tggcactgtt 360
 gtaatganaa tcttcactgt a 381

<210> 453
 <211> 455
 <212> DNA
 <213> Homo sapiens

<400> 453
 actgtgctaa acagcctata gccaaagttt aaagagttac aggaacaact gctacacatt 60
 caaagaacag gcattcactg cagcctcctg atttgacctg atgggaggga caggagaatg 120
 agtcaactctg ccaccacttt tcctgccttg gattttaga ggatttgtt tgccttaatt 180
 tgtttttcct atatctgccc tactaaaggta cacagtctgg gcactttgaa aatgttaaag 240
 tttttaacgt ttgactgaca gaagcagcac ttaaaggcct catgaatcta ttttccaaaa 300
 aaagtatgct ttcagtaaaa cattttacca ttttatctaa ctatgcaactg acatttttgt 360
 tcttcctgaa aaggggattt atgctaacac tgtattttta atgtaaaaat atacgtgtag 420
 agatatatta acttcctgag tgacttatac ctcaa 455

<210> 454
 <211> 383
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(383)
 <223> n = A,T,C or G

<400> 454
 acagagcanc tttacaagtt gtcacatttc tttataaatt tttttaagc tacagttaa 60
 tacaaaatga attgcggtt tattacatta ataaccttc acctcagggt tttatgaaga 120
 ggaaaggggt ttatgcaaaa gaaagtgcta caattcctaa tcattttaga cacttttaga 180
 ggggggtgaag ttgtatgata aagcagatat ttttaattatt tgttatcttt ttgtattgca 240

120

```

agaaatttct tgctagttaa tcaagaaaac atccagattg acagtctaaa atggctactg 300
gtatttttagt taattcaaaa atgaaacttt tcagtgtatc actttactaa cattctatct 360
gagaaggcctt attggtaaaag ttt                                     383

```

```

<210> 455
<211> 383
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

```

```

<400> 455
actcctttan gacaaggaaa caggatcag catgatggta gcagaaacct tatcaccaag 60
gtgcaggagc tgacttcttc caaagagttg tggttccggg cagcggtcat tgccgtgccc 120
attgctggag ggctgatttt agtggtgctt attatgttgg ccctgaggat gcttcgaagt 180
gaaaataaga ggctgcagga tcagcggcaa cagatgctct cccgtttgca ctacagcttt 240
cacggacacc attccaaaaa ggggcagggt gcaaagttag acttggaatg catggtgccg 300
gtcagtgggc acgagaactg ctgtctgacc tgtgataaaa tgagacaagc agacctcagc 360
aacgataaga tcctctcgct tgt                                     383

```

```

<210> 456
<211> 543
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(543)
<223> n = A,T,C or G

```

```

<400> 456
acaaacattt tacaaaaaag aacattacca atatcagtg cagtaagggc aagctgaaga 60
atangtagac tgagtttccg ggcaatgtct gtcctcaaa acatccaaac tgcgttcagg 120
cagctgaaac aggttctttt ccagtgaca agcatatgtg gtcagtaata caaacgatgg 180
taaataaggc tactacatag gccaggttaa caaactcctc ttctcctcgg gtaggccatg 240
atacaagtgg aactcatcaa ataattttaa cccaaggcga taacaacact atttcccatc 300
taaaactcatt taagccttca caatgtcgca atggattcag ttacttgcaa acgatcccgg 360
gttgtcatat agtactttgt tttttacaca taacgctgtg ccatcccttc cttcactgcc 420
ccagtcagggt ttctgtttgt tggaccgaaa ggggatacat tttagaaatg cttccctcaa 480
gacagaagtg agaaagaaaag gagaccctga ggccaggatc tattaacact ggtgtgtgcg 540
caa                                     543

```

```

<210> 457
<211> 544
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(544)
<223> n = A,T,C or G

```

```

<400> 457
actggtgccat atattgncat ggtgagctcc tctctaattgt cttccagggc accaatatct 60
gcccatgtca cattagggac agtgacaaag ctttcccttt tggcagaggg ttggactgag 120
gatagagcaa caatgaaatc attcagttca atgcacagtc cttgcatctg ctctctgag 180
aggggatctt ggtctcttag caacccagc agccttttga attcatcctg tgtttcagaa 240
gtgggctcag ttcccagcct ttcctcctgg actcctttag atggcaaata ttccatttca 300
ggatttttct tctgctgttc ctgtagcttc attaagactc tattgactgc acacattgct 360

```

121

```

gcctctcggc acagtgccat gagatcagca ccaacaaagc ctggagttag gtgtgctaag 420
tgacagaaat caaaagcttg aggaagcctc agttttctgc acaatgtttg aagtattctt 480
tccttggaat cttcatctgg gatacctagg catatttctc ggtcgaacct tccgcacagt 540
ctca                                         544

```

```

<210> 458
<211> 382
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(382)
<223> n = A,T,C or G

```

```

<400> 458
acctntaggc tcaacggcag aancctcacc acaaaagcga aatgggcaca ccacagggag 60
aaaactgggt gtcttggaat ttgaaaagt tgggtcgttg catggtgtgt tacttcatcc 120
tatctatcat taactccatg gcacaaagtt atgccaaacg aatccagcag cggttgaact 180
cagaggagaa aactaaataa gtagagaaaag ttttaaaactg cagaaattgg agtggatggg 240
ttctgcctta aattgggagg actccaagcc gggaaggaaa attccctttt ccaacctgta 300
tcaattttta caactttttt cctgaaagca gttagtcca tactttgcac tgacatactt 360
tttccttctg tgctaaggta ag                                         382

```

```

<210> 459
<211> 168
<212> DNA
<213> Homo sapiens

```

```

<400> 459
ctcgtactct agccaggcac gaaaccatga agtagcctga tccttcttag ccatacctggc 60
cgcttagcgt gtagtaactt tgtgttatga atcacatgaa agcatggaat cttatgaact 120
taatcccttc attaacagga gaaatgcaaa taccttcata tccccctca          168

```

```

<210> 460
<211> 190
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(190)
<223> n = A,T,C or G

```

```

<400> 460
acanctgcta ccaggagacc gagagctgac tatccagacc tcggctaatt tattctacgc 60
catggatgga gcttcacacg atttcctcct gcggcagcgg cgaaggctct ctactgctac 120
acctggcgct accagtggcc cgtctgcctc aggaactcct ccgagtgagg gaggaggggg 180
ctcctttccc                                         190

```

```

<210> 461
<211> 495
<212> DNA
<213> Homo sapiens

```

```

<400> 461
acagacaggc ttctctgcta tcctccaggc agtgtaatat tcaaggaaaa gggcaacagt 60
attggatcat tccttagaca ctaatcagct ggggaaagag ttcataggca aaagtgtcct 120
ccaagaatg gtttacacca agcagagagg acatgtcact gaatggggaa agggaacccc 180
cgtatccaca gtcactgtaa gcatccagta ggcaggaaga tggctttggg cagtggctgg 240
atgaaagcag atttgagata cccagctccg gaacgaggtc atcttctaca ggttcttctt 300
tcactgagac aatgaattca gggatgatcat tctctgaggg gctgagaggt gcttctctga 360

```

122

```

ttttcactac cacattagct tggctctctg tctcagaggg tatctctaag actaggggct 420
tgggtatatat gtgggtcaaaa cgaattagtt cattaatggc ttccagcttg gctgatgacg 480
tccccactga cagag                                     495

```

```

<210> 462
<211> 493
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(493)
<223> n = A,T,C or G

```

```

<400> 462
acactgaaac ataaatccgc aagtcaccac acatacaaca cccggcagga aaaaaacaaa 60
aacagggngt ttacatgata cctgtaacag ccatgggtctc aaactcagat gcttcctcca 120
tctgccaagt gtgttttgga tacagagcac atcgtggcct ctgggggtcac actcagctta 180
ggctgtgggt ccacagagca ctcactctgg tgggctatgg tgggtgggtgc tctactcaag 240
aagcaaaagca gttaccagca cattcaaaaca gtgtattgaa catcttttaa atatcaaaagt 300
gagaaacaag aaggcaacat aataatgtta tcagaaagat gttaggaaagt aaggacagct 360
gtgtaaaagt tgaggttgaa aagtagcttg ccagcttcat ttctttgggt tcttgggtag 420
tggggcgccg aacagcaaga tgtgaggttc tggttcatgg atcatataat ggacccatcc 480
ctgactctgc tga                                     493

```

```

<210> 463
<211> 3681
<212> DNA
<213> Homo sapiens

```

```

<400> 463
tccgagctga ttacagacac caaggaagat gctgtaaaga gtcagcagcc acagccctgg 60
ctagctggcc ctgtgggcat ttattagtaa agttttaatg acaaaagctt tgagtcaaca 120
caccctgggg taattaacct ggtcatcccc accctggaga gccatcctgc ccatgggtga 180
tcaaagaagg aacatctgca ggaacacctg atgaggctgc acccttggcg gaaagaacac 240
ctgacacagc tgaaagcttg gtggaaaaaa cactgatga ggctgcaccc ttggtggaaa 300
gaacacctga cacggctgaa agcttgggtg aaaaaacacc tgatgaggct gcctccttgg 360
tggaggggaa atctgacaaa attcaatgtt tggagaaagc gacatctgga aagttcgaac 420
agtccagcaga agaaacacct agggaaatta cgagtcctgc aaaagaaaaca tctgagaaat 480
ttacgtggcc agcaaaagga agacctagga agatcgcatg ggagaaaaaa gaagacacac 540
ctaggggaaat tatgagtcac gcaaaagaaa catctgagaa atttacgtgg gcagcaaaag 600
gaagacctag gaagatcgca tgggagaaaa aagaaacacc tgtaaagact ggatgcgtgg 660
caagagtaac atctaataaa actaaagttt tggaaaaagg aagatctaag atgattgcat 720
gtcctacaaa agaactcatc acaaaagcaa tgccaatga tcagaggttc ccatcagaat 780
ccaaacaaga ggaagatgaa gaattattct gtgattctcg gagtctcttt gagagtctcg 840
caaagattca agtgtgtata cctgagtcta tatatcaaaa agtaatggag ataaatagag 900
aagtagaaga gcctcctaag aagccatctg ccttcaagcc tgccattgaa atgcaaaact 960
ctgttccaaa taaagccttt gaattgaaga atgaacaaac attgagagca gatccgatgt 1020
tcccaccaga atccaaacaa aaggactatg aagaaaattc ttgggattct gagagtctct 1080
gtgagactgt ttacacagaag gatgtgtgtt taccacaggc tacacatcaa aaagaaatag 1140
ataaaataaa tggaaaatta gaagagtctc ctaataaaga tggctctctg aaggctacct 1200
gcggaatgaa agtttctatt ccaactaaag ccttagaatt gaaggacatg caaactttca 1260
aagcagagcc tccggggaag ccatctgcct tcgagcctgc cactgaaatg caaaagtctg 1320
tcccaaataa agccttggaa ttgaaaaatg aacaaacatt gagagcagat gagatactcc 1380
catcagaatc caaacaaaag gactatgaag aaagtctctg ggattctgag agtctctgtg 1440
agactgtttc acagaaggat gtgtgtttac ccaaggctrc rcatcaaaaa gaaatagata 1500
aaataaatgg aaaattagaa ggttctcctg ttaaagatgg tcttctgaag gctaactgag 1560
gaatgaaagt ttctattcca actaaagcct tagaattgat ggacatgcaa actttcaaag 1620
cagagcctcc cgagaagcca tctgccttcg agcctgccat tgaaatgcaa aagtctgttc 1680
caaataaagc cttggaattg aagaatgaac aaacattgag agcagatgag atactcccat 1740
cagaatccaa acaaaaggac tatgaagaaa gttcttggga ttctgagagt ctctgtgaga 1800
ctgtttcaca gaaggatgtg tgtttaccca aggctrcrca tcaaaaagaa atagataaaa 1860

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taaatggaaa	attagaagag	tctcctgata	atgatggttt	tctgaaggct	ccctgcagaa	1920
tgaaagtttc	tattccaact	aaagccttag	aattgatgga	catgcaaact	ttcaaagcag	1980
agcctcccga	gaagccatct	gccttcgagc	ctgccattga	aatgcaaaag	tctgttccaa	2040
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aatcaaaaca	aaagaasgtt	gaagaaaatt	cttgggattc	tgagagtctc	cgtgagactg	2160
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gtggaaaatt	agaagattca	actagcctat	caaaaatctt	ggatacagtt	cattcttctg	2280
aaagagcaag	ggaacttcaa	aaagatcact	gtgaacaacg	tacaggaaaa	atggaacaaa	2340
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agttagagaa	ccaaaaagtt	aaatgggaac	aagagctctg	cagtgtgagg	tttctcacac	2460
tcatgaaaat	gaaaattatc	tcttacatga	aaattgcatg	ttgaaaaagg	aaattgccat	2520
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tgaggacatt	aagattttta	aagaaaagaa	tgctgaactt	cagatgaccc	taaaactgaa	2640
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tgagaacaca	atgctcactt	ctaattgaa	ggaaaaacaa	gacaaagaaa	tactagaggc	2760
agaaattgaa	tcacaccatc	ctagactggc	ttctgctgta	caagaccatg	atcaaattgt	2820
gacatcaaga	aaaagtcaag	aacctgcttt	ccacattgca	ggagatgctt	gtttgcaaag	2880
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ttctgaagct	gaaagaaaat	ccaaaagcct	aaaaattaat	ctcaattatg	cmggagatgc	3000
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tcacacgcaa	ttagttcatg	cacataagaa	agctgacaac	aaaagcaaga	taacaattga	3240
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aacagaaaac	tcatgagaga	caagcagtaa	gaaacttctt	ttggagaaac	aacagaccag	3420
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taccaatagt	ctgtgtcaac	agaatactta	ttttagaaga	aaaattcatg	atttcttctc	3540
gaagcctaca	gacataaaat	aacagtgtga	agaattactt	gttcacgaat	tgcataaagc	3600
tgacacaggat	tcccatctac	cctgatgatg	cagcagacat	cattcaatcc	aaccagaatc	3660
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<210> 464

<211> 1424

<212> DNA

<213> Homo sapiens

<400> 464

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cacccgtggg	taattaacct	ggatcatccc	accctggaga	gccatcctgc	ccatgggtga	180
tcaaagaagg	aacatctgca	ggaacacctg	atgaggctgc	acccttggcg	gaaagaacac	240
ctgacacagc	tgaaagcttg	gtggaaaaaa	cacctgatga	ggctgcaccc	ttggtggaaa	300
gaacacctga	cacggctgaa	agcttgggtg	aaaaaacacc	tgatgaggct	gcaccccttg	360
tgaggggaac	atctgacaaa	attcaatgtt	tgagagaaag	gacatctgga	aagttcgaac	420
agtcagcaga	agaaacacct	agggaaatta	cgagtcctgc	aaaagaaaca	tctgagaaat	480
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ctaggggaaat	tatgagtccc	gcaaaagaaa	catctgagaa	atttacgtgg	gcagcaaaag	600
gaagacctag	gaagatcgca	tgggagaaaa	aagaaacacc	tgtaaagact	ggatgcgtgg	660
caagagtaac	atctaataaa	actaaagttt	tgaaaaaagg	aagatctaag	atgattgcat	720
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tgttggcaac	agactatatt	gagagtgtctg	aaaaggagct	gaattattag	tttgaattca	1380
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124

<210> 465
<211> 674
<212> DNA
<213> Homo sapiens

<400> 465
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cacacccgtg ggtaattaac ctggatcatcc ccaccctgga gagccatcct gcccatgggt 180
gatcaaaagaa ggaacatctg caggaacacc tgatgaggct gcacccttgg cgaaagaac 240
acctgacaca gctgaaagct tgggtgaaaa aacacctgat gaggtgcac ccttggtgga 300
aagaacacct gacacggctg aaagcttggg ggaaaaaaca cctgatgagg ctgcatcctt 360
ggtggaggga acatctgaca aaattcaatg tttggagaaa gcgacatctg gaaagtctga 420
acagtcagca gaagaaacac ctagggaat tacgagtcct gcaaaagaaa catctgagaa 480
atttacgtgg ccagcaaaag gaagacctag gaagatcgca tgggagaaaa aagatgactc 540
agttaaggca aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660
aaaaaaaaaa aaaa 674

<210> 466
<211> 1729
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (11)
<223> n=A,T,C or G
<221> unsure
<222> (1128)
<223> n=A,T,C or G

<400> 466
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aagaagacac acctagggaa attatgagtc ccgcaaaaga aacatctgag aaatttacgt 180
gggcagcaaa aggaagacct aggaagatcg catgggagaa aaaagaaaca cctgtaaaaga 240
ctggatgcgt ggcaagagta acatctaata aaactaaagt tttggaaaaa ggaagatcta 300
agatgattgc atgtcctaca aaagaatcat ctacaaaagc aagtgcctat gatcagaggt 360
tcccatcaga atccaaacaa gaggaagatg aagaatattc ttgtgattct cggagtctct 420
ttgagagtgc tgcaaaagatt caagtgtgta tacctgagtc tatatatcaa aaagtaatgg 480
agataaatag agaagtagaa gagcctccta agaagccatc tgccttcaag cctgccattg 540
aaatgcaaaa ctctgttcca aataaaagcct ttgaattgaa gaatgaacaa acattgagag 600
cagatccgat gttcccacca gaatccaaac aaaaggacta tgaagaaaat tcttgggatt 660
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aaaaagaaat agataaaata aatggaaaat tagaagagtc tcctaataaa gatggctctc 780
tgaaggctac ctgcggaatg aaagtttcta ttccaactaa agccttagaa ttgaaggaca 840
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aaatagataa aataaatgga aaattagaag gtaagaaccg ttttttatth aaaaatcatt 1500
tgaccaataa tttctctaaa ttgatgagga aggatatcct ctagtagctg aagaaaaata 1560
cctcctaaat gcaaaccatg gaaaaaaga gaagtgaat ggtcataagc tatgtgtctc 1620
atcaggcatt ggcaacagac tatattgtga gtgctgaaga ggagctgaat tactagttta 1680

aattcaagat attccaagac gtgaggaaaa tgagaaaaaa aaaaaaaaaa 1729

<210> 467

<211> 1337

<212> DNA

<213> Homo sapiens

<400> 467

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tgcaaaacttt caaagcagag cctcccgaga agccatctgc cttcgcgcct gccattgaaa 180
tgcaaaagtc tgttccaaat aaagccttgg aattgaagaa tgaacaaaca ttgagagcag 240
atgagatact cccatcagaa tccaaacaaa aggactatga agaaagtctt tgggattctg 300
agagtctctg tgagactgtt tcacagaagg atgtgtgttt acccaaggct gcgcacaaa 360
aagaaataga taaaataaat ggaaaattag aagagtctcc tgataatgat ggttttctga 420
aggctccctg cagaatgaaa gtttctattc caactaaagc cttagaattg atggacatgc 480
aaactttcaa agcagagcct cccgagaagc catctgcctt cgagcctgcc attgaaatgc 540
aaaagtctgt tccaaataaa gccttggaat tgaagaatga acaaacattg agagcagatc 600
agatgttccc tcagaatca aaacaaaaga aggttgaaaga aaattcttgg gattctgaga 660
gtctccgtga gactgtttca cagaaggatg tgtgtgtacc caaggctaca catcaaaaaa 720
aaatggataa aataagtgga aaattagaag attcaactag cctatcaaaa atcttgata 780
cagttcattc ttgtgaaaga gcaagggaac ttcaaaaaga tcaactgtga caacgtacag 840
gaaaaatgaa acaaatgaaa aagaagtttt gtgtactgaa aaagaaactg tcagaagcaa 900
aagaaataaa atcacagtta gagaacccaa aagttaaatg ggaacaagag ctctgcagtg 960
tgagattgac tttaaaccaa gaagaagaga agagaagaaa tgccgatata ttaaatgaaa 1020
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aacaactgaa acaggctctc agaatacaag atatagaatt gaagagtgtg gaaagtaatt 1140
tgaaatcaggt ttctcacact catgaaaatg aaaattatct cttacatgaa aattgcattg 1200
tgaaaaagga aattgccatg ctaaaactgg aaatagccac actgaaacac caataccagg 1260
aaaaggaaaa taaatacttt gaggacatta agatttttaa agaaaagaat gctgaacttc 1320
agatgacccc tcgtgcc 1337

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<210> 468

<211> 2307

<212> DNA

<213> Homo sapiens

<400> 468

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tacacatcaa aaagaaatag ataaaaataa tgaaaaatta gaagggtctc ctgttaaaga 180
tggtcttctg aaggctaact gcggaatgaa agtttctatt ccaactaaag ccttagaatt 240
gatggacatg caaactttca aagcagagcc tcccgagaag ccactcgcct tcgagcctgc 300
cattgaaatg caaaagtctg ttccaaataa agccttgaa ttgaagaatg aacaaacatt 360
gagagcagat gagatactcc catcagaatc caacaaaag gactatgaag aaagttcttg 420
ggattctgag agtctctgtg agactgtttc acagaaggat gtgtgtttac ccaaggctac 480
acatcaaaaa gaaatagata aaataaatgg aaaattagaa gagtctcctg ataattgatg 540
ttttctgaag tctccctgca gaatgaaagt ttctattcca actaaagcct tagaattgat 600
ggacatgcaa actttcaaag cagagcctcc cgagaagcca tctgccttcg agcctgccat 660
tgaaatgcaa aagtctgttc caaataaagc cttggaattg aagaatgaac aaacattgag 720
agcagatcag atgttccctt cagaatcaaa acaaaagaac gttgaagaaa attcttgga 780
ttctgagagt ctccgtgaga ctgtttcaca gaaggatgtg tgtgtaccca aggctacaca 840
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<220>
<221> unsure
<222> (310)
<223> Xaa = Any Amino Acid
<221> unsure
<222> (429)
<223> Xaa = Any Amino Acid
<221> unsure
<222> (522)
<223> Xaa = Any Amino Acid
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<400> 469																
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Gly	Arg	Pro	Arg ₂₀	Lys	Ile	Ala	Trp	Glu ₂₅	Lys	Lys	Glu	Thr	Pro ₃₀	Val	Lys	
Thr	Gly ₃₅	Cys	Val	Ala	Arg	Val	Thr ₄₀	Ser	Asn	Lys	Thr	Lys ₄₅	Val	Leu	Glu	
Lys	Gly ₅₀	Arg	Ser	Lys	Met	Ile ₅₅	Ala	Cys	Pro	Thr	Lys ₆₀	Glu	Ser	Ser	Thr	
Lys ₆₅	Ala	Ser	Ala	Asn	Asp ₇₀	Gln	Arg	Phe	Pro	Ser ₇₅	Glu	Ser	Lys	Gln	Glu ₈₀	
Glu	Asp	Glu	Glu	Tyr ₈₅	Ser	Cys	Asp	Ser	Arg ₉₀	Ser	Leu	Phe	Glu	Ser	Ser ₉₅	
Ala	Lys	Ile	Gln ₁₀₀	Val	Cys	Ile	Pro	Glu ₁₀₅	Ser	Ile	Tyr	Gln	Lys ₁₁₀	Val	Met	
Glu	Ile ₁₁₅	Asn	Arg	Glu	Val	Glu	Glu ₁₂₀	Pro	Pro	Lys	Lys	Pro	Ser	Ala	Phe	
Lys ₁₃₀	Pro	Ala	Ile	Glu	Met	Gln	Asn ₁₃₅	Ser	Val	Pro	Asn ₁₄₀	Lys	Ala	Phe	Glu	
Leu ₁₄₅	Lys	Asn	Glu	Gln	Thr ₁₅₀	Leu	Arg	Ala	Asp	Pro ₁₅₅	Met	Phe	Pro	Pro	Glu ₁₆₀	
Ser	Lys	Gln	Lys	Asp ₁₆₅	Tyr	Glu	Glu	Asn	Ser ₁₇₀	Trp	Asp	Ser	Glu	Ser	Leu ₁₇₅	
Cys	Glu	Thr	Val ₁₈₀	Ser	Gln	Lys	Asp	Val ₁₈₅	Cys	Leu	Pro	Lys	Ala ₁₉₀	Thr	His	
Gln	Lys ₁₉₅	Glu	Ile	Asp	Lys	Ile	Asn ₂₀₀	Gly	Lys	Leu	Glu	Glu	Ser	Pro	Asn	
Lys	Asp ₂₁₀	Gly	Leu	Leu	Lys	Ala ₂₁₅	Thr	Cys	Gly	Met	Lys ₂₂₀	Val	Ser	Ile	Pro	
Thr	Lys	Ala	Leu	Glu	Leu	Lys	Asp	Met	Gln	Thr	Phe	Lys	Ala	Glu	Pro	

127

225					230					235				240
Pro	Gly	Lys	Pro	Ser	Ala	Phe	Glu	Pro	Ala	Thr	Glu	Met	Gln	Lys
				245					250					255
Val	Pro	Asn	Lys	Ala	Leu	Glu	Leu	Lys	Asn	Glu	Gln	Thr	Leu	Arg
			260					265					270	
Asp	Glu	Ile	Leu	Pro	Ser	Glu	Ser	Lys	Gln	Lys	Asp	Tyr	Glu	Glu
		275					280				285			
Ser	Trp	Asp	Ser	Glu	Ser	Leu	Cys	Glu	Thr	Val	Ser	Gln	Lys	Asp
	290				295					300				
Cys	Leu	Pro	Lys	Ala	Xaa	His	Gln	Lys	Glu	Ile	Asp	Lys	Ile	Asn
305					310					315				320
Lys	Leu	Glu	Gly	Ser	Pro	Val	Lys	Asp	Gly	Leu	Leu	Lys	Ala	Asn
			325						330					335
Gly	Met	Lys	Val	Ser	Ile	Pro	Thr	Lys	Ala	Leu	Glu	Leu	Met	Asp
			340					345					350	
Gln	Thr	Phe	Lys	Ala	Glu	Pro	Pro	Glu	Lys	Pro	Ser	Ala	Phe	Glu
		355					360					365		
Ala	Ile	Glu	Met	Gln	Lys	Ser	Val	Pro	Asn	Lys	Ala	Leu	Glu	Leu
	370					375					380			
Asn	Glu	Gln	Thr	Leu	Arg	Ala	Asp	Glu	Ile	Leu	Pro	Ser	Glu	Ser
385					390					395				400
Gln	Lys	Asp	Tyr	Glu	Glu	Ser	Ser	Trp	Asp	Ser	Glu	Ser	Leu	Cys
			405						410					415
Thr	Val	Ser	Gln	Lys	Asp	Val	Cys	Leu	Pro	Lys	Ala	Xaa	His	Gln
			420					425					430	
Glu	Ile	Asp	Lys	Ile	Asn	Gly	Lys	Leu	Glu	Glu	Ser	Pro	Asp	Asn
		435					440					445		
Gly	Phe	Leu	Lys	Ala	Pro	Cys	Arg	Met	Lys	Val	Ser	Ile	Pro	Thr
	450					455					460			
Ala	Leu	Glu	Leu	Met	Asp	Met	Gln	Thr	Phe	Lys	Ala	Glu	Pro	Pro
465					470					475				480
Lys	Pro	Ser	Ala	Phe	Glu	Pro	Ala	Ile	Glu	Met	Gln	Lys	Ser	Val
			485						490					495
Asn	Lys	Ala	Leu	Glu	Leu	Lys	Asn	Glu	Gln	Thr	Leu	Arg	Ala	Asp
			500					505					510	
Met	Phe	Pro	Ser	Glu	Ser	Lys	Gln	Lys	Xaa	Val	Glu	Glu	Asn	Ser
	515						520					525		Trp
Asp	Ser	Glu	Ser	Leu	Arg	Glu	Thr	Val	Ser	Gln	Lys	Asp	Val	Cys
	530					535					540			Val
Pro	Lys	Ala	Thr	His	Gln	Lys	Glu	Met	Asp	Lys	Ile	Ser	Gly	Lys
545					550					555				560
Glu	Asp	Ser	Thr	Ser	Leu	Ser	Lys	Ile	Leu	Asp	Thr	Val	His	Ser
			565						570					575
Glu	Arg	Ala	Arg	Glu	Leu	Gln	Lys	Asp	His	Cys	Glu	Gln	Arg	Thr
			580					585					590	Gly
Lys	Met	Glu	Gln	Met	Lys	Lys	Lys	Phe	Cys	Val	Leu	Lys	Lys	Lys
		595					600					605		Leu
Ser	Glu	Ala	Lys	Glu	Ile	Lys	Ser	Gln	Leu	Glu	Asn	Gln	Lys	Val
	610					615					620			Lys
Trp	Glu	Gln	Glu	Leu	Cys	Ser	Val	Arg	Phe	Leu	Thr	Leu	Met	Lys
625					630					635				640
Lys	Ile	Ile	Ser	Tyr	Met	Lys	Ile	Ala	Cys					
				645					650					

<210> 470

<211> 228

<212> PRT

<213> Homo sapiens

<400> 470

Met Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Ala Ala Lys

128

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Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr Pro Val Lys
      20      25      30
Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu
      35      40      45
Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr
      50      55      60
Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu
      65      70      75      80
Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser
      85      90      95
Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met
      100      105      110
Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe
      115      120      125
Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu
      130      135      140
Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu
      145      150      155      160
Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu
      165      170      175
Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His
      180      185      190
Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Gly Lys Asn Arg
      195      200      205
Phe Leu Phe Lys Asn Gln Leu Thr Glu Tyr Phe Ser Lys Leu Met Arg
      210      215      220
Arg Asp Ile Leu
225

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<210> 471
 <211> 154
 <212> PRT
 <213> Homo sapiens

<220>
 <221> unsure
 <222> (148)
 <223> Xaa = Any Amino Acid

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<400> 471
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      20      25      30
Leu Thr Arg Leu Lys Ala Trp Trp Lys Lys His Leu Met Arg Leu His
      35      40      45
Pro Trp Trp Arg Glu His Leu Thr Lys Phe Asn Val Trp Arg Lys Arg
      50      55      60
His Leu Glu Ser Ser Asn Ser Gln Gln Lys Lys His Leu Gly Lys Leu
      65      70      75      80
Arg Val Leu Gln Lys Lys His Leu Arg Asn Leu Arg Gly Gln Gln Lys
      85      90      95
Glu Asp Leu Gly Arg Ser His Gly Arg Lys Lys Met Thr Gln Leu Arg
      100      105      110
Gln Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
      115      120      125
Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
      130      135      140
Lys Lys Lys Xaa Lys Lys Lys Lys Lys Lys
145      150

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129

<210> 472
 <211> 466
 <212> PRT
 <213> Homo sapiens

<220>
 <221> unsure
 <222> (329)
 <223> Xaa = Any Amino Acid

<400> 472

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      20      25      30
Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu
      35      40      45
Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr
      50      55      60
Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu
      65      70      75      80
Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser
      85      90      95
Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met
      100      105      110
Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe
      115      120      125
Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu
      130      135      140
Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu
      145      150      155      160
Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu
      165      170      175
Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His
      180      185      190
Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asn
      195      200      205
Lys Asp Gly Leu Leu Lys Ala Thr Cys Gly Met Lys Val Ser Ile Pro
      210      215      220
Thr Lys Ala Leu Glu Leu Lys Asp Met Gln Thr Phe Lys Ala Glu Pro
      225      230      235      240
Pro Gly Lys Pro Ser Ala Phe Glu Pro Ala Thr Glu Met Gln Lys Ser
      245      250      255
Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala
      260      265      270
Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Asn
      275      280      285
Ser Trp Asp Thr Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val
      290      295      300
Cys Leu Pro Lys Ala Ala His Gln Lys Glu Ile Asp Lys Ile Asn Gly
      305      310      315      320
Lys Leu Glu Gly Ser Pro Gly Lys Xaa Gly Leu Leu Lys Ala Asn Cys
      325      330      335
Gly Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met
      340      345      350
Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro
      355      360      365
Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys
      370      375      380
Asn Glu Gln Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys

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130

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385          390          395          400
Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu
          405          410          415
Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Ala His Gln Lys
          420          425          430
Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Gly Lys Asn Arg Phe Leu
          435          440          445
Phe Lys Asn His Leu Thr Lys Tyr Phe Ser Lys Leu Met Arg Lys Asp
          450          455          460
Ile Leu
465

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<210> 473
<211> 445
<212> PRT
<213> Homo sapiens

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<400> 473
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Asp Gly Leu Leu Lys Ala Asn Cys Gly Met Lys Val Ser Ile Pro Thr
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Lys Ala Leu Glu Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro
          35          40          45
Glu Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val
          50          55          60
Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp
          65          70          75          80
Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser Ser
          85          90          95
Trp Asp Ser Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys
          100          105          110
Leu Pro Lys Ala Ala His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys
          115          120          125
Leu Glu Glu Ser Pro Asp Asn Asp Gly Phe Leu Lys Ala Pro Cys Arg
          130          135          140
Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met Gln
          145          150          155          160
Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala
          165          170          175
Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn
          180          185          190
Glu Gln Thr Leu Arg Ala Asp Gln Met Phe Pro Ser Glu Ser Lys Gln
          195          200          205
Lys Lys Val Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu Arg Glu Thr
          210          215          220
Val Ser Gln Lys Asp Val Cys Val Pro Lys Ala Thr His Gln Lys Glu
          225          230          235          240
Met Asp Lys Ile Ser Gly Lys Leu Glu Asp Ser Thr Ser Leu Ser Lys
          245          250          255
Ile Leu Asp Thr Val His Ser Cys Glu Arg Ala Arg Glu Leu Gln Lys
          260          265          270
Asp His Cys Glu Gln Arg Thr Gly Lys Met Glu Gln Met Lys Lys Lys
          275          280          285
Phe Cys Val Leu Lys Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys Ser
          290          295          300
Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser Val
          305          310          315          320
Arg Leu Thr Leu Asn Gln Glu Glu Glu Lys Arg Arg Asn Ala Asp Ile
          325          330          335
Leu Asn Glu Lys Ile Arg Glu Glu Leu Gly Arg Ile Glu Glu Gln His

```

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<210> 474
<211> 3865
<212> DNA
<213> Homo sapien

<220>
<221> misc feature
<222> (2448)...(2631)
<223> 184 bp insert of B726P splice form
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caccctggg	taattaaact	ggtcatcccc	accctggaga	gccatctctg	ccatgggtga	180
tcaaagaagg	aacatctgca	ggaacacctg	atgaggctgc	acccttggcg	gaaagaaacac	240
ctgacacagc	tgaagagctt	gtggaaaaaa	cacctgatga	ggctgcaccc	ttggtggaaa	300
gaacacctga	cacggctgaa	agcttgggtg	aaaaaacacc	tgatgagggt	gcactcttgg	360
tggagggaac	atctgacaaa	attcaatgtt	tggagaaga	gacatcttga	aagttcgaac	420
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ctagggaaat	tatgagtcct	gcaaaagaaa	catctgagaa	atttacgtgg	gcagcaaaag	600
gaagacctag	gaagatcgca	tgggagaaaa	aagaacacac	tgtaaagact	ggatgcgtgg	660
caagagtaac	attctaataa	actaaagtgt	tggaaaaagg	agatcttaag	atgattgcac	720
gtcctacaaa	agaatcatct	acaaaagcaa	gtgccaatga	tcagagggtt	ccatcagaat	780
ccaaacaaga	ggaagatgaa	gaatatctct	gtgattctcg	gagtcctctt	gagagttctg	840
caaagattca	agtggtgata	cctgagtcct	tatatcaaaa	agtaattggag	ataaatagag	900
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aatctcgctc tgtcactcag gctgg 3865

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<210> 475

<211> 1002

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(1002)

<223> Xaa = Any Amino Acid

<400> 475

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Met Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Ala Ala Lys
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Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr Pro Val Lys
 20          25          30
Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu
 35          40          45
Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr
 50          55          60
Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu
 65          70          75          80
Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser
 85          90          95
Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met
 100          105          110
Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe
 115          120          125
Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu
 130          135          140
Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu
 145          150          155          160
Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu
 165          170          175

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Cys	Glu	Thr	Val	Ser	Gln	Lys	Asp	Val	Cys	Leu	Pro	Lys	Ala	Thr	His
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Gln	Lys	Glu	Ile	Asp	Lys	Ile	Asn	Gly	Lys	Leu	Glu	Glu	Ser	Pro	Asn
		195					200					205			
Lys	Asp	Gly	Leu	Leu	Lys	Ala	Thr	Cys	Gly	Met	Lys	Val	Ser	Ile	Pro
	210					215					220				
Thr	Lys	Ala	Leu	Glu	Leu	Lys	Asp	Met	Gln	Thr	Phe	Lys	Ala	Glu	Pro
225					230				235						240
Pro	Gly	Lys	Pro	Ser	Ala	Phe	Glu	Pro	Ala	Thr	Glu	Met	Gln	Lys	Ser
				245					250					255	
Val	Pro	Asn	Lys	Ala	Leu	Glu	Leu	Lys	Asn	Glu	Gln	Thr	Leu	Arg	Ala
			260					265					270		
Asp	Glu	Ile	Leu	Pro	Ser	Glu	Ser	Lys	Gln	Lys	Asp	Tyr	Glu	Glu	Ser
		275					280					285			
Ser	Trp	Asp	Ser	Glu	Ser	Leu	Cys	Glu	Thr	Val	Ser	Gln	Lys	Asp	Val
	290					295					300				
Cys	Leu	Pro	Lys	Ala	Xaa	His	Gln	Lys	Glu	Ile	Asp	Lys	Ile	Asn	Gly
305					310					315					320
Lys	Leu	Glu	Gly	Ser	Pro	Val	Lys	Asp	Gly	Leu	Leu	Lys	Ala	Asn	Cys
				325					330					335	
Gly	Met	Lys	Val	Ser	Ile	Pro	Thr	Lys	Ala	Leu	Glu	Leu	Met	Asp	Met
			340					345					350		
Gln	Thr	Phe	Lys	Ala	Glu	Pro	Pro	Glu	Lys	Pro	Ser	Ala	Phe	Glu	Pro
		355					360					365			
Ala	Ile	Glu	Met	Gln	Lys	Ser	Val	Pro	Asn	Lys	Ala	Leu	Glu	Leu	Lys
	370					375					380				
Asn	Glu	Gln	Thr	Leu	Arg	Ala	Asp	Glu	Ile	Leu	Pro	Ser	Glu	Ser	Lys
385					390					395					400
Gln	Lys	Asp	Tyr	Glu	Glu	Ser	Ser	Trp	Asp	Ser	Glu	Ser	Leu	Cys	Glu
			405						410					415	
Thr	Val	Ser	Gln	Lys	Asp	Val	Cys	Leu	Pro	Lys	Ala	Xaa	His	Gln	Lys
			420					425					430		
Glu	Ile	Asp	Lys	Ile	Asn	Gly	Lys	Leu	Glu	Glu	Ser	Pro	Asp	Asn	Asp
		435					440					445			
Gly	Phe	Leu	Lys	Ala	Pro	Cys	Arg	Met	Lys	Val	Ser	Ile	Pro	Thr	Lys
	450					455					460				
Ala	Leu	Glu	Leu	Met	Asp	Met	Gln	Thr	Phe	Lys	Ala	Glu	Pro	Pro	Glu
465					470					475					480
Lys	Pro	Ser	Ala	Phe	Glu	Pro	Ala	Ile	Glu	Met	Gln	Lys	Ser	Val	Pro
				485					490					495	
Asn	Lys	Ala	Leu	Glu	Leu	Lys	Asn	Glu	Gln	Thr	Leu	Arg	Ala	Asp	Gln
			500				505						510		
Met	Phe	Pro	Ser	Glu	Ser	Lys	Gln	Lys	Xaa	Val	Glu	Glu	Asn	Ser	Trp
		515					520					525			
Asp	Ser	Glu	Ser	Leu	Arg	Glu	Thr	Val	Ser	Gln	Lys	Asp	Val	Cys	Val
	530					535					540				
Pro	Lys	Ala	Thr	His	Gln	Lys	Glu	Met	Asp	Lys	Ile	Ser	Gly	Lys	Leu
545					550					555					560
Glu	Asp	Ser	Thr	Ser	Leu	Ser	Lys	Ile	Leu	Asp	Thr	Val	His	Ser	Cys
			565						570					575	
Glu	Arg	Ala	Arg	Glu	Leu	Gln	Lys	Asp	His	Cys	Glu	Gln	Arg	Thr	Gly
			580					585					590		
Lys	Met	Glu	Gln	Met	Lys	Lys	Lys	Phe	Cys	Val	Leu	Lys	Lys	Lys	Leu
		595					600					605			
Ser	Glu	Ala	Lys	Glu	Ile	Lys	Ser	Gln	Leu	Glu	Asn	Gln	Lys	Val	Lys
	610					615					620				
Trp	Glu	Gln	Glu	Leu	Cys	Ser	Val	Arg	Leu	Thr	Leu	Asn	Gln	Glu	Glu
625					630					635					640
Glu	Lys	Arg	Arg	Asn	Ala	Asp	Ile	Leu	Asn	Glu	Lys	Ile	Arg	Glu	Glu
				645					650					655	
Leu	Gly	Arg	Ile	Glu	Glu	Gln	His	Arg	Lys	Glu	Leu	Glu	Val	Lys	Gln
			660					665					670		

134

Gln Leu Glu Gln Ala Leu Arg Ile Gln Asp Ile Glu Leu Lys Ser Val
 675 680 685
 Glu Ser Asn Leu Asn Gln Val Ser His Thr His Glu Asn Glu Asn Tyr
 690 695 700
 Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys
 705 710 715 720
 Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys Glu Asn Lys
 725 730 735
 Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala Glu Leu Gln
 740 745 750
 Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg Ala Ser Gln
 755 760 765
 Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr Met Leu Thr
 770 775 780
 Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu Ala Glu Ile
 785 790 795 800
 Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp His Asp Gln
 805 810 815
 Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His Ile Ala Gly
 820 825 830
 Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser Ser Thr Ile
 835 840 845
 Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala Gln Arg Lys
 850 855 860
 Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp Ala Leu Arg
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 Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln Arg Glu Thr
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 Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn Glu Gln Asp
 900 905 910
 Asn Val Asn Lys His Thr Glu Gln Glu Ser Leu Asp Gln Lys Leu
 915 920 925
 Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln Leu Val His
 930 935 940
 Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile Asp Ile His
 945 950 955 960
 Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu Lys Asn Glu
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<210> 476

<211> 356

<212> DNA

<213> Homo sapien

<400> 476

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tgcactttga aagaccctc cactccttg cctcacattt ctctgtgtga tccccactt      180
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<210> 477

<211> 1876

<212> DNA

<213> Homo sapien

<400> 477

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aaaaaaaa aaaaaa 1876

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<210> 478

<211> 505

<212> PRT

<213> Homo sapien

<400> 478

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          20          25          30
Arg Gly Ile Ser Cys Tyr Arg Gly Leu Thr Gly Gly Phe Gly Ser His
          35          40          45
Ser Val Cys Gly Gly Phe Arg Ala Gly Ser Cys Gly Arg Ser Phe Gly
          50          55          60
Tyr Arg Ser Gly Gly Val Cys Gly Pro Ser Pro Cys Ile Thr Thr
65          70          75          80
Val Ser Val Asn Glu Ser Leu Leu Thr Pro Leu Asn Leu Glu Ile Asp
          85          90          95
Pro Asn Ala Gln Cys Val Lys Gln Glu Glu Lys Glu Gln Ile Lys Ser
          100          105          110
Leu Asn Ser Arg Phe Ala Ala Phe Ile Asp Lys Val Arg Phe Leu Glu
          115          120          125
Gln Gln Asn Lys Leu Leu Glu Thr Lys Leu Gln Phe Tyr Gln Asn Arg
          130          135          140
Glu Cys Cys Gln Ser Asn Leu Glu Pro Leu Phe Glu Gly Tyr Ile Glu
145          150          155          160
Thr Leu Arg Arg Glu Ala Glu Cys Val Glu Ala Asp Ser Gly Arg Leu
          165          170          175
Ala Ser Glu Leu Asn His Val Gln Glu Val Leu Glu Gly Tyr Lys Lys

```


136

				180					185					190			
Lys	Tyr	Glu	Glu	Glu	Val	Ser	Leu	Arg	Ala	Thr	Ala	Glu	Asn	Glu	Phe		
		195					200					205					
Val	Ala	Leu	Lys	Lys	Asp	Val	Asp	Cys	Ala	Tyr	Leu	Arg	Lys	Ser	Asp		
		210				215					220						
Leu	Glu	Ala	Asn	Val	Glu	Ala	Leu	Ile	Gln	Glu	Ile	Asp	Phe	Leu	Arg		
225					230					235					240		
Arg	Leu	Tyr	Glu	Glu	Ile	Arg	Ile	Leu	Gln	Ser	His	Ile	Ser	Asp			
				245					250					255			
Thr	Ser	Val	Val	Val	Lys	Leu	Asp	Asn	Ser	Arg	Asp	Leu	Asn	Met	Asp		
			260					265						270			
Cys	Ile	Ile	Ala	Glu	Ile	Lys	Ala	Gln	Tyr	Asp	Asp	Ile	Val	Thr	Arg		
		275					280					285					
Ser	Arg	Ala	Glu	Ala	Glu	Ser	Trp	Tyr	Arg	Ser	Lys	Cys	Glu	Glu	Met		
		290				295					300						
Lys	Ala	Thr	Val	Ile	Arg	His	Gly	Glu	Thr	Leu	Arg	Arg	Thr	Lys	Glu		
305					310					315					320		
Glu	Ile	Asn	Glu	Leu	Asn	Arg	Met	Ile	Gln	Arg	Leu	Thr	Ala	Glu	Val		
				325					330					335			
Glu	Asn	Ala	Lys	Cys	Gln	Asn	Ser	Lys	Leu	Glu	Ala	Ala	Val	Ala	Gln		
			340					345					350				
Ser	Glu	Gln	Gln	Gly	Glu	Ala	Ala	Leu	Ser	Asp	Ala	Arg	Cys	Lys	Leu		
		355				360						365					
Ala	Glu	Leu	Glu	Gly	Ala	Leu	Gln	Lys	Ala	Lys	Gln	Asp	Met	Ala	Cys		
		370				375					380						
Leu	Ile	Arg	Glu	Tyr	Gln	Glu	Val	Met	Asn	Ser	Lys	Leu	Gly	Leu	Asp		
385					390					395					400		
Ile	Glu	Ile	Ala	Thr	Tyr	Arg	Arg	Leu	Leu	Glu	Gly	Glu	Glu	Gln	Arg		
				405					410					415			
Leu	Cys	Glu	Gly	Ile	Gly	Ala	Val	Asn	Val	Cys	Val	Ser	Ser	Ser	Arg		
		420						425					430				
Gly	Gly	Val	Val	Cys	Gly	Asp	Leu	Cys	Val	Ser	Gly	Ser	Arg	Pro	Val		
		435				440						445					
Thr	Gly	Ser	Val	Cys	Ser	Ala	Pro	Cys	Asn	Gly	Asn	Val	Ala	Val	Ser		
		450				455					460						
Thr	Gly	Leu	Cys	Ala	Pro	Cys	Gly	Gln	Leu	Asn	Thr	Thr	Cys	Gly	Gly		
465					470					475				480			
Gly	Ser	Cys	Gly	Val	Gly	Ser	Cys	Gly	Ile	Ser	Ser	Leu	Gly	Val	Gly		
				485					490					495			
Ser	Cys	Gly	Ser														

```
<210> 479
<211> 221
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> (1)...(221)
<223> n = A,T,C or G
```

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<400> 479
gggtccattcc tttcctcgcg tnggggtttc tctgtgtcag cgagcctcgg tacactgatt 60
tccgatcaaa agaatcatca tcttttacct gacttttcag ggaattactg aacttttcttc 120
tcagaagata gggcacagcc attgcctttg cctcatttga agggtctgca tttgggtcct 180
ctgggtctctt gccaaagtttc ccagccactc gaggagaaaa t                221
```

<210> 480
<211> 36
<212> DNA .

137

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 480

cggcgaattc accatgggaa caagagctct gcagtg

36

<210> 481

<211> 62

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 481

cggcaagctt ttaatggtga tggatgatgt gtataacttc tgtttctgct ttctcttttt 60
ca 62

<210> 482

<211> 972

<212> DNA

<213> Homo sapiens

<400> 482

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atgggaacaa gagctctgca gtgtgaggtt tctcacactc atgaaaatga aaattatctc 60
ttacatgaaa attgcatgtt gaaaaaggaa attgccatgc taaaactgga aatagccaca 120
ctgaaacacc aataccagga aaaggaaaat aaatactttg aggacattaa gatttttaaaa 180
gaaaagaatg ctgaacttca gatgacccta aaactgaaaag aggaatcatt aactaaaagg 240
gcactctcaat atagtgggca gcttaaagtt ctgatagctg agaacacaat gctcacttct 300
aaattgaagg aaaaacaaga caaagaaata ctagaggcag aaattgaatc acaccatcct 360
agactggctt ctgctgtaca agaccatgat caaattgtga catcaagaaa aagtcaagaa 420
cctgctttcc acattgcagg agatgcttgt ttgcaaagaa aaatgaatgt tgatgtgagt 480
agtacgatat ataacaatga ggtgctccat caaccacttt ctgaagctca aaggaaatcc 540
aaaagcctaa aaattaatct caattatgcc ggagatgctc taagagaaaa tacattgggt 600
tcagaacatg cacaagaga ccaacgtgaa acacagtgtc aaatgaagga agctgaacac 660
atgtatcaaa acgaacaaga taatgtgaac aaacacactg aacagcagga gtctctagat 720
cagaaattat ttcaactaca aagcaaaaat atgtggcttc aacagcaatt agttcatgca 780
cataagaaag ctgacaaca aagcaagata acaattgata ttcattttct tgagaggaaa 840
atgcaacatc atctcctaaa agagaaaaat gaggagatat ttaattacaa taaccattta 900
aaaaaccgta tatatcaata tgaaaaagag aaagcagaaa cagaagttat acatcatcac 960
catcaccatt aa 972

```

<210> 483

<211> 323

<212> PRT

<213> Homo sapiens

<400> 483

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Met Gly Thr Arg Ala Leu Gln Cys Glu Val Ser His Thr His Glu Asn
      5              10              15
Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala
      20              25              30
Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys
      35              40              45
Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala
      50              55              60
Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg
      65              70              75              80
Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr

```

[illegible]

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<210> 484
<211> 1518
<212> DNA
<213> Homo sapiens
```

<400>	484						
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cggcccgggcc	gctgtgtgcat	caccgcgcgcc	ccctaccgtg	gcattctcgt	ctaccgcgggc	120	
ctcacccggg	gcttcggcag	ccacacgcgtg	tgcggaggct	ttcgggcggg	ctctcgcgga	180	
cgcagcttcg	gctaccgcctc	cgggggcgtg	tgcgggccca	gtcccccatg	catcaccacc	240	
gtgtcgtgta	acgagagcct	cctcacgcgcc	ctcaaccttg	agatcgacc	caacgcgcga	300	
tgcgtgaagc	aggaggagaa	ggagcagatc	aagtcctcta	acagcaggtt	cgcggccttc	360	
atcgacaagg	tgcgtcttct	ggagcagcag	aacaaactgc	tggagacaaa	gctgcagttc	420	
taccagaacc	gcgagtgttg	ccagagcaac	ctggagcccc	tgtttgaggg	ctcatcgcag	480	
actctgcggc	gggaggccga	gtgcgtggag	gccgacagcg	ggaggctggc	ctcagagctt	540	
aaccacgtgc	aggaggtgct	ggagggtctac	aagaagaagt	atgaggagga	ggtttctctg	600	
agagcaacag	ctgagaacga	gtttgtggct	ctgaagaagc	atgtggactg	cgcctacctc	660	
gcgaagttag	acctgtaggc	caactgtggg	gacctgacg	aggagatcga	cttctctagg	720	
cggctgtatg	aggaggagat	ccgcattctc	cagtcgcaca	tctcagacac	ctcgttggtt	780	
gtcaagctgg	acaaacagcc	ggacctgaac	atggactcga	tcattgccga	gattaaggga	840	
cagtatgcag	acattgtcac	cgcagcccg	gccgagccg	agtcctggta	cgcagcaag	900	
tgtaggagaa	tgaaggccac	ggtgatcagg	cacggggaga	ccctcgcggc	caccaaggag	960	
gagatcaatg	agctgaaccg	catgatccaa	aggctgacgg	ccgaggtgga	gaatgccaag	1020	
tgccagaact	ccaagctgga	ggccgcgggt	gccacgtctg	agcagcaggg	tgagcgagcc	1080	
ctcagtgtatg	cccgtgcgaa	gctggccgag	ctggaggggc	ccctgcagaa	ggccaagcac	1140	
gacatggcct	gcctgatcag	ggagttaccag	gaggtgatga	actccaagct	gggcctggac	1200	
atcgagatcg	ccacctacag	gcgcctgctg	gagggcgagg	agcagaggct	atgtgaaggc	1260	
atgtgggctg	tgaatgtctg	tgtcagcagc	tcccggttgc	gggtcgtgtg	cggggacctc	1320	
tgcgtgtcag	gctcccggcc	agtgaactgg	agtgtctgca	gcgctccgtg	caacgggaac	1380	
gtggcgttga	gcaccggcct	gtgtgcgccc	tgcggccaat	tgaaccaccac	ctctcggagg	1440	

139

ggttcctgcg gcgtgggctc ctgtgggtatc agctccctgg gtgtggggtc ttgcggcagc 1500
 agctgccgga aatgttag 1518

<210> 485

<211> 505

<212> PRT

<213> Homo sapiens

<400> 485

Met Thr Cys Gly Ser Gly Phe Gly Gly Arg Ala Phe Arg Cys Ile Ser
 5 10 15
 Ala Cys Gly Pro Arg Pro Gly Arg Cys Cys Ile Thr Ala Ala Pro Tyr
 20 25 30
 Arg Gly Ile Ser Cys Tyr Arg Gly Leu Thr Gly Gly Phe Gly Ser His
 35 40 45
 Ser Val Cys Gly Gly Phe Arg Ala Gly Ser Cys Gly Arg Ser Phe Gly
 50 55 60
 Tyr Arg Ser Gly Gly Val Cys Gly Pro Ser Pro Cys Ile Thr Thr
 65 70 75 80
 Val Ser Val Asn Glu Ser Leu Leu Thr Pro Leu Asn Leu Glu Ile Asp
 85 90 95
 Pro Asn Ala Gln Cys Val Lys Gln Glu Lys Glu Gln Ile Lys Ser
 100 105 110
 Leu Asn Ser Arg Phe Ala Ala Phe Ile Asp Lys Val Arg Phe Leu Glu
 115 120 125
 Gln Gln Asn Lys Leu Leu Glu Thr Lys Leu Gln Phe Tyr Gln Asn Arg
 130 135 140
 Glu Cys Cys Gln Ser Asn Leu Glu Pro Leu Phe Glu Gly Tyr Ile Glu
 145 150 155 160
 Thr Leu Arg Arg Glu Ala Glu Cys Val Glu Ala Asp Ser Gly Arg Leu
 165 170 175
 Ala Ser Glu Leu Asn His Val Gln Glu Val Leu Glu Gly Tyr Lys Lys
 180 185 190
 Lys Tyr Glu Glu Glu Val Ser Leu Arg Ala Thr Ala Glu Asn Glu Phe
 195 200 205
 Val Ala Leu Lys Lys Asp Val Asp Cys Ala Tyr Leu Arg Lys Ser Asp
 210 215 220
 Leu Glu Ala Asn Val Glu Ala Leu Ile Gln Glu Ile Asp Phe Leu Arg
 225 230 235 240
 Arg Leu Tyr Glu Glu Ile Arg Ile Leu Gln Ser His Ile Ser Asp
 245 250 255
 Thr Ser Val Val Val Lys Leu Asp Asn Ser Arg Asp Leu Asn Met Asp
 260 265 270
 Cys Ile Ile Ala Glu Ile Lys Ala Gln Tyr Asp Asp Ile Val Thr Arg
 275 280 285
 Ser Arg Ala Glu Ala Glu Ser Trp Tyr Arg Ser Lys Cys Glu Glu Met
 290 295 300
 Lys Ala Thr Val Ile Arg His Gly Glu Thr Leu Arg Arg Thr Lys Glu
 305 310 315 320
 Glu Ile Asn Glu Leu Asn Arg Met Ile Gln Arg Leu Thr Ala Glu Val
 325 330 335
 Glu Asn Ala Lys Cys Gln Asn Ser Lys Leu Glu Ala Val Ala Gln
 340 345 350
 Ser Glu Gln Gln Gly Glu Ala Ala Leu Ser Asp Ala Arg Cys Lys Leu
 355 360 365
 Ala Glu Leu Glu Gly Ala Leu Gln Lys Ala Lys Gln Asp Met Ala Cys
 370 375 380
 Leu Ile Arg Glu Tyr Gln Glu Val Met Asn Ser Lys Leu Gly Leu Asp
 385 390 395 400
 Ile Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly Glu Glu Arg
 405 410 415
 Leu Cys Glu Gly Ile Gly Ala Val Asn Val Cys Val Ser Ser Ser Arg

140

```

      420      425      430
Gly Gly Val Cys Gly Asp Leu Cys Val Ser Gly Ser Arg Pro Val
      435      440      445
Thr Gly Ser Val Cys Ser Ala Pro Cys Asn Gly Asn Val Ala Val Ser
      450      455      460
Thr Gly Leu Cys Ala Pro Cys Gly Gln Leu Asn Thr Thr Cys Gly Gly
465      470      475      480
Gly Ser Cys Gly Val Gly Ser Cys Gly Ile Ser Ser Leu Gly Val Gly
      485      490      495
Ser Cys Gly Ser Ser Cys Arg Lys Cys
      500      505

```

<210> 486
 <211> 827
 <212> DNA
 <213> Homo sapiens

```

<400> 486
gcattctcca gtcgcacatc tcagacacct ccgtggttgt caagctggac aacagccggg 60
acctgaacat ggactgcacg attgccgaga ttaaggcaca gtatgacgac attgtcaccc 120
gcagccgggc cgaggccgag tcctggtacc gcagcaagtg tgaggagatg aaggccacgg 180
tgatcaggca cggggagacc ctgcccgcga ccaaggagga gatcaatgag ctgaaccgca 240
tgatccaaag gctgacggcc gaggtggaga atgccaagtg ccagaactcc aagctggagg 300
ccgcggtggc ccagtctgag cagcaggggt aggcagccct cagtgatgcc cgctgcaagc 360
tgcccagact ggagggcgcc ctgcagaagg ccaagcagga catggcctgc ctgatcaggg 420
agtaccagga ggtgatgaac tccaagctgg gcctggacat cgagatcgcc acctacaggc 480
gcctgctgga gggcgaggag cagaggctat gtgaaggcat tggggctgtg aatgtctgtg 540
tcagcagctc ccggggcggg gtcgtgtgcg gggacctctg cgtgtcaggc tcccggccag 600
tgactggcag tgtctgcagc gctccgtgca acgggaacgt ggcggtgagc accggcctgt 660
gtgcgccctg cggccaattg aacaccacct gcggaggggg ttccctgcggc gtgggctcct 720
gtggatatcag ctccctgggt gtggggtctt gcggcagcag ctgccgaaa tgtaggcac 780
cccaactcaa gtcccaggcc ccaggcatct ttcctgcctt gccttgc 827

```

<210> 487
 <211> 235
 <212> PRT
 <213> Homo sapiens

```

<400> 487
Met Asp Cys Ile Ile Ala Glu Ile Lys Ala Gln Tyr Asp Asp Ile Val
      5      10      15
Thr Arg Ser Arg Ala Glu Ala Glu Ser Trp Tyr Arg Ser Lys Cys Glu
      20      25      30
Glu Met Lys Ala Thr Val Ile Arg His Gly Glu Thr Leu Arg Arg Thr
      35      40      45
Lys Glu Glu Ile Asn Glu Leu Asn Arg Met Ile Gln Arg Leu Thr Ala
      50      55      60
Glu Val Glu Asn Ala Lys Cys Gln Asn Ser Lys Leu Glu Ala Ala Val
      65      70      75      80
Ala Gln Ser Glu Gln Gln Gly Glu Ala Ala Leu Ser Asp Ala Arg Cys
      85      90      95
Lys Leu Ala Glu Leu Glu Gly Ala Leu Gln Lys Ala Lys Gln Asp Met
      100      105      110
Ala Cys Leu Ile Arg Glu Tyr Gln Glu Val Met Asn Ser Lys Leu Gly
      115      120      125
Leu Asp Ile Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly Glu Glu
      130      135      140
Gln Arg Leu Cys Glu Gly Ile Gly Ala Val Asn Val Cys Val Ser Ser
      145      150      155      160
Ser Arg Gly Gly Val Val Cys Gly Asp Leu Cys Val Ser Gly Ser Arg
      165      170      175

```

141

Pro Val Thr Gly Ser Val Cys Ser Ala Pro Cys Asn Gly Asn Val Ala
 180 185 190
 Val Ser Thr Gly Leu Cys Ala Pro Cys Gly Gln Leu Asn Thr Thr Cys
 195 200 205
 Gly Gly Gly Ser Cys Gly Val Gly Ser Cys Gly Ile Ser Ser Leu Gly
 210 215 220
 Val Gly Ser Cys Gly Ser Ser Cys Arg Lys Cys
 225 230 235

<210> 488
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 488
 Ser Leu Thr Lys Arg Ala Ser Gln Tyr
 5

<210> 489
 <211> 27

<212> DNA
 <213> Homo sapiens

<400> 489
 tcattaacta aaaggcatc tcaatat

27

<210> 490
 <211> 3288
 <212> DNA
 <213> Homo sapiens

<400> 490
 atgaagttgc tgaatgtcct catgctggcg gccctctccc agcactgcta cgcaggctct 60
 ggctgcccc tattggagaa tgtgatttcc aagacaatca atccacaagt gtctaagact 120
 gaatacaaa aacttcttca agagttcata gacgacaatg ccactacaaa tgccatagat 180
 gaattgaagg aatgttttct taaccaaacg gatgaaactc tgagcaatgt tgagggtgtt 240
 atgcaattaa tatatgacag cagtctttgt gatttattta tgagtcccg aaaagaaaca 300
 tctgagaaat ttacgtggcg agcaaaagga agacctagga agatcgcatg ggagaaaaaa 360
 gaaacacctg taaagactgg atgctgtgca agagtaacat ctaataaaac taaagttttg 420
 gaaaaaggaa gatctaagat gattgcatgt cctacaaaag aatcatctac aaaagcaagt 480
 gccaatgatc agaggttccc atcagaatcc aaacaagagg aagatgaaga atattcttgt 540
 gattctcgga gtctctttga gatttctgca aagattcaag tgtgtatacc tgagtctata 600
 tatcaaaaag taatggagat aaatagagaa gtagaagagc ctccataaga gccatctgcc 660
 ttcaagcctg ccattgaaat gcaaaactct gttccaaata aagcctttga attgaagaat 720
 gaacaaacat tgagagcaga tccgatgttc ccaccagaat ccaaaacaaa ggactatgaa 780
 gaaaattctt gggattctga gagtctctgt gagactgttt cacagaagga tgtgtgttta 840
 ccaaggcta cecatcaaaa agaaatagat aaaataaatg gaaaattaga agagtctcct 900
 aataaagatg gtcttctgaa ggctacctgc ggaatgaaag tttctattcc aactaaagcc 960
 ttagaattga aggacatgca aactttcaaa gcagagcctc cggggaagcc atctgccttc 1020
 gagcctgcca ctgaaatgca aaagtctgtc ccaaataaag ccttgggaatt gaaaaatgaa 1080
 caaacattga gagcagatga gatactccca tcagaatcca aacaaaagga ctatgaagaa 1140
 agttcttggg attctgagag tctctgtgag actgtttcac agaaggatgt gtgtttaccc 1200
 aaggctrcrc atcaaaaaaga aatagataaa ataaatggaa aattagaagg gtctcctgtt 1260
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 gaattgatgg acatgcaaac tttcaagca gagcctccc agaaagccatc tgccttcgag 1380
 cctgccattg aaatgcaaaa gtctgttcca aataaagcct tggaattgaa gaatgaacaa 1440
 acattgagag cagatgagat actcccatca gaatccaaac aaaaggacta tgaagaaagt 1500
 tcttgggatt ctgagagtct ctgtgagact gtttcacaga aggatgtgtg tttacccaag 1560
 gctrcrcatc aaaaagaaat agataaaata aatggaaaat tagaagagtc tcctgataat 1620

gatgggttttc	tgaaggctcc	ctgcagaatg	aaagtttcta	ttccaactaa	agccttagaa	1680
ttgatggaca	tgcaaaacttt	caaagcagag	cctcccagaga	agccatctgc	cttcgagcct	1740
gccattgaaa	tgcaaaagtc	tgttccaaat	aaagccttgg	aattgaagaa	tgaacaaaca	1800
ttgagagcag	atcagatgtt	cccttcagaa	tcaaaacaaa	agaasgttga	agaaaattct	1860
tgaggattctg	agagctctcg	tgagactgtt	tcacagaagg	atgtgtgtgt	acccaaggct	1920
acacatcaaa	aagaaatgga	taaaataagt	ggaaaattag	aagattcaac	tagcctatca	1980
aaaatcttgg	atacagttca	ttcttgtgaa	agagcaaggg	aacttcaaaa	agatcactgt	2040
gaacaacgta	caggaaaaat	ggaacaaatg	aaaaagaagt	tttgtgtact	gaaaaagaaa	2100
ctgtcagaag	caaaagaaat	aaaatcacag	ttagagaacc	aaaaagttaa	atgggaacaa	2160
gagctctgca	gtgtgagatt	gacttttaac	caagaagaag	agaagagaag	aaatgccgat	2220
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ttagaagtga	aacaacaact	tgaacaggct	ctcagaatac	aagatataga	attgaagagt	2340
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gaaaattgca	tggtgaaaaa	ggaaattgcc	atgctaaaac	tggaaatagc	cacactgaaa	2460
caccaatacc	aggaaaagga	aaataaatac	tttgaggaca	ttaagatttt	aaaagaaaag	2520
aatgctgaac	ttcagatgac	cctaataactg	aaagaggaat	cattaactaa	aagggcactc	2580
caatatagtg	ggcagcttaa	agttctgata	gctgagaaca	caatgctcac	ttctaaattg	2640
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gcttctgctg	tacaagacca	tgatcaaatt	gtgacatcaa	gaaaaagtca	agaacctgtc	2760
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ctaaaaatta	atctcaatta	tgcmggagat	gctctaagag	aaaatacatt	ggtttcagaa	2940
catgcacaaa	gagaccaacg	tgaacacacg	tgtcaaatga	aggaagctga	acacatgtat	3000
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ttatttcaac	tacaagcaaa	aaatatgtgg	cttcaacagc	aattagttca	tgacacataa	3120
aaagctgaca	acaaaagcaa	gataacaatt	gatattcatt	ttcttgagag	gaaaatgcaa	3180
catcatctcc	taaaagagaa	aatgaggag	atatttaatt	acaataacca	tttaaaaaac	3240
cgtatatatc	aatatgaaaa	agagaaagca	gaaacagaaa	actcatga		3288

<210> 491

<211> 2232

<212> DNA

<213> Homo sapiens

<400> 491

atgaagttgc	tgatggctcc	catgctggcg	gccctctccc	agcactgcta	cgcaggctct	60
ggctgccctt	tattggagaa	tgatgattcc	aagacaatca	atccacaagt	gtctaagact	120
gaatacaaa	aacttcttca	agagttcata	gacgacaatg	ccactacaaa	tgccatagat	180
gaattgaagg	aatgttttct	taaccaaacg	gatgaaactc	tgagcaatgt	tgaggtgttt	240
atgcaattaa	tatatgacag	cagtctttgt	gatttattta	tgagtcctcg	aaaagaaaca	300
tctgagaaat	ttactgtggc	agcaaaagga	agacctagga	agatcgcatg	ggagaaaaaa	360
gaaacacctg	taaaagactg	atgctgtggc	agagtaacat	ctaataaaac	ttaaagttttg	420
gaaaaaggaa	gatctaagat	gattgcatgt	cctacaaaag	aatcatctac	aaaagcaagt	480
gccaatgatc	agaggttccc	atcagaatcc	aaacaagagg	aagatgaaga	atattcttgt	540
gattctcgga	gtctctttga	gagttctgca	aagattcaag	tgtgtatacc	tgagtctata	600
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ttcaagcctg	ccattgaaat	gcaaaactct	gttccaaata	aagcctttga	attgaagaat	720
gaacaaacat	tgagagcaga	tccgatgttc	ccaccagaat	ccaaacaaaa	ggactatgaa	780
gaaaattctt	gggattctga	gagtcctctg	gagactgttt	cacagaagga	tgtgtgttta	840
cccaaggcta	cacatcaaaa	agaaatagat	aaaataaatg	gaaaattaga	agagtctcct	900
aataaagatg	gtcttctgaa	ggctacctgc	ggaatgaaag	tttctattcc	aactaaagcc	960
ttagaattga	aggacatgca	aactttcaaa	gcagagcctc	cggggaagcc	atctgccttc	1020
gagcctgcc	ctgaaatgca	aaagtctgtc	ccaataaag	ccttgggaat	gaaaaatgaa	1080
caaacattga	gagcagatga	gatactccca	tcagaatcca	aacaaaagga	ctatgaagaa	1140
agttcttggg	attctgagag	tctctgtgag	actgtttcac	agaaggatgt	gtgtttaccc	1200
aaggctrcrc	atcaaaaaga	aatagataaa	ataaatggaa	aattagaagg	gtctcctgtt	1260
aaagatgggt	ttctgaaggc	taactgcgga	atgaaagttt	ctattccaac	ttaaagcctta	1320
gaattgatgg	acatgcaaac	tttcaaaagc	gagcctcccg	agaagccatc	tgcttctgag	1380
cctgccattg	aaatgcaaaa	gtctgtttcca	aataaagcct	tggaattgaa	gaatgaacaa	1440
acattgagag	cagatgagat	actcccatca	gaatccaaac	aaaaggacta	tgaagaaagt	1500
tcttgggatt	ctgagagtct	ctgtgagact	gtttcacaga	aggatgtgtg	tttaccacaa	1560
gctrcrcatc	aaaaagaaat	agataaaata	aatggaaaat	tagaagagtc	tcctgataat	1620

143

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gatgggttttc tgaaggctcc ctgcagaatg aaagtttcta ttccaactaa agccttagaa 1680
ttgatggaca tgcaaaacttt caaagcagag cctcccgaga agccatctgc cttcgagcct 1740
gccattgaaa tgcaaaagtc tgttccaaat aaagccttgg aattgaagaa tgaacaaaca 1800
ttgagagcag atcagatggt cccttcagaa tcaaaacaaa agaasgttga agaaaattct 1860
tgggattctg agagtctccg tgagactggt tcacagaagg atgtgtgtgt acccaaggct 1920
acacatcaaaa aagaaatgga taaaataagt ggaaaattag aagattcaac tagcctatca 1980
aaaatcttgg atacagtcca ttcttgtgaa agagcaaggg aacttcaaaa agatcactgt 2040
gaacaacgta caggaaaaat ggaacaaatg aaaaagaagt tttgtgtact gaaaaagaaa 2100
ctgtcagaag caaaagaaat aaaatcacag ttagagaacc aaaaagttaa atgggaacaa 2160
gagctctgca gtgtgagggt tctcacactc atgaaaatga aaattatctc ttacatgaaa 2220
attgcatggt ga 2232

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<210> 492

<211> 1233

<212> DNA

<213> Homo sapiens

<400> 492

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atgaagttgc tgatggtcct catgctggcg gccctctccc agcactgcta cgcaggctct 60
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gaatacaaa aacttcttca agagttcata gacgacaatg ccactacaaa tgccatagat 180
gaattgaagg aatgttttct taaccaaacy gatgaaactc tgagcaatgt tgagggtgtt 240
atgcaattaa tatatgacag cagtctttgt gatttattta tgggaacaag agctctgcag 300
tgtgagggtt ctcacactca tgaaaatgaa aattatctct tacatgaaa ttgcatgttg 360
aaaaaggaaa ttgccatgct aaaactggaa atagccacac tgaaacacca ataccaggaa 420
aaggaaaaata aacttttga ggacattaag attttaaaag aaaagaatgc tgaacttcag 480
atgaccctaa aactgaaaga ggaatcatta actaaaaggg catctcaata tagtgggcag 540
cttaaaagttc tgatagctga gaacacaatg ctcaattcta aattgaagga aaaacaagac 600
aaagaaatac tagaggcaga aattgaatca caccatccta gactggcttc tgctgtacaa 660
gaccatgatc aaattgtgac atcaagaaaa agtcaagaac ctgctttcca cattgcagga 720
gatgcttggt tgcaaaagaaa aatgaatgtt gatgtgagta gtacgatata taacaatgag 780
gtgctccatc accactttc tgaaagctcaa aggaaatcca aaagcctaaa aattaatctc 840
aattatgccg gagatgctct aagagaaaaat acattggttt cagaacatgc acaaagagac 900
caacgtgaaa cacagtgtca aatgaaggaa gctgaacaca tgtatcaaaa cgaacaagat 960
aatgtgaaca aacacactga acagcaggag tctctagatc agaaattatt tcaactacaa 1020
agcaaaataa tgtggcttca acagcaatta gttcatgcac ataagaaagc tgacaacaaa 1080
agcaagataa caattgatat tcttttctt gagagaaaaa tgcaacatca tctcctaaaa 1140
gagaaaaaat aggagatatt taattacaat aaccatttaa aaaaccgtat atatcaatat 1200
gaaaaagaga aagcagaac agaagttata taa 1233

```

<210> 493

<211> 1095

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> (1)...(1095)

<223> Xaa = Any amino acid

<400> 493

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Met Lys Leu Leu Met Val Leu Met Leu Ala Ala Leu Ser Gln His Cys
      5      10      15
Tyr Ala Gly Ser Gly Cys Pro Leu Leu Glu Asn Val Ile Ser Lys Thr
      20      25      30
Ile Asn Pro Gln Val Ser Lys Thr Glu Tyr Lys Glu Leu Leu Gln Glu
      35      40      45
Phe Ile Asp Asp Asn Ala Thr Thr Asn Ala Ile Asp Glu Leu Lys Glu
      50      55      60
Cys Phe Leu Asn Gln Thr Asp Glu Thr Leu Ser Asn Val Glu Val Phe
      65      70      75      80
Met Gln Leu Ile Tyr Asp Ser Ser Leu Cys Asp Leu Phe Met Ser Pro

```


					85						90						95
Ala	Lys	Glu	Thr	Ser	Glu	Lys	Phe	Thr	Trp	Ala	Ala	Lys	Gly	Arg	Pro		
					100						105						110
Arg	Lys	Ile	Ala	Trp	Glu	Lys	Lys	Glu	Thr	Pro	Val	Lys	Thr	Gly	Cys		
					115						120						125
Val	Ala	Arg	Val	Thr	Ser	Asn	Lys	Thr	Lys	Val	Leu	Glu	Lys	Gly	Arg		
					130						135						140
Ser	Lys	Met	Ile	Ala	Cys	Pro	Thr	Lys	Glu	Ser	Lys	Thr	Lys	Ala	Ser		
					145						150						155
Ala	Asn	Asp	Gln	Arg	Phe	Pro	Ser	Glu	Ser	Lys	Gln	Glu	Glu	Asp	Glu		
					165						170						175
Glu	Tyr	Ser	Cys	Asp	Ser	Arg	Ser	Leu	Phe	Glu	Ser	Ser	Ala	Lys	Ile		
					180						185						190
Gln	Val	Cys	Ile	Pro	Glu	Ser	Ile	Tyr	Gln	Lys	Val	Met	Glu	Ile	Asn		
					195						200						205
Arg	Glu	Val	Glu	Glu	Pro	Pro	Lys	Lys	Pro	Ser	Ala	Phe	Lys	Pro	Ala		
					210						215						220
Ile	Glu	Met	Gln	Asn	Ser	Val	Pro	Asn	Lys	Ala	Phe	Glu	Leu	Lys	Asn		
					225						230						235
Glu	Gln	Thr	Leu	Arg	Ala	Asp	Pro	Met	Phe	Pro	Pro	Glu	Ser	Lys	Gln		
					245						250						255
Lys	Asp	Tyr	Glu	Glu	Asn	Ser	Trp	Asp	Ser	Glu	Ser	Leu	Cys	Glu	Thr		
					260						265						270
Val	Ser	Gln	Lys	Asp	Val	Cys	Leu	Pro	Lys	Ala	Thr	His	Gln	Lys	Glu		
					275						280						285
Ile	Asp	Lys	Ile	Asn	Gly	Lys	Leu	Glu	Glu	Ser	Pro	Asn	Lys	Asp	Gly		
					290						295						300
Leu	Leu	Lys	Ala	Thr	Cys	Gly	Met	Lys	Val	Ser	Ile	Pro	Thr	Lys	Ala		
					305						310						315
Leu	Glu	Leu	Lys	Asp	Met	Gln	Thr	Phe	Lys	Ala	Glu	Pro	Pro	Gly	Lys		
					325						330						335
Pro	Ser	Ala	Phe	Glu	Pro	Ala	Thr	Glu	Met	Gln	Lys	Ser	Val	Pro	Asn		
					340						345						350
Lys	Ala	Leu	Glu	Leu	Lys	Asn	Glu	Gln	Thr	Leu	Arg	Ala	Asp	Glu	Ile		
					355						360						365
Leu	Pro	Ser	Glu	Ser	Lys	Gln	Lys	Asp	Tyr	Glu	Glu	Ser	Ser	Trp	Asp		
					370						375						380
Ser	Glu	Ser	Leu	Cys	Glu	Thr	Val	Ser	Gln	Lys	Asp	Val	Cys	Leu	Pro		
					385						390						395
Lys	Ala	Xaa	His	Gln	Lys	Glu	Ile	Asp	Lys	Ile	Asn	Gly	Lys	Leu	Glu		
					405						410						415
Gly	Ser	Pro	Val	Lys	Asp	Gly	Leu	Leu	Lys	Ala	Asn	Cys	Gly	Met	Lys		
					420						425						430
Val	Ser	Ile	Pro	Thr	Lys	Ala	Leu	Glu	Leu	Met	Asp	Met	Gln	Thr	Phe		
					435						440						445
Lys	Ala	Glu	Pro	Pro	Glu	Lys	Pro	Ser	Ala	Phe	Glu	Pro	Ala	Ile	Glu		
					450						455						460
Met	Gln	Lys	Ser	Val	Pro	Asn	Lys	Ala	Leu	Glu	Leu	Lys	Asn	Glu	Gln		
					465						470						475
Thr	Leu	Arg	Ala	Asp	Glu	Ile	Leu	Pro	Ser	Glu	Ser	Lys	Gln	Lys	Asp		
					485						490						495
Tyr	Glu	Glu	Ser	Ser	Trp	Asp	Ser	Glu	Ser	Leu	Cys	Glu	Thr	Val	Ser		
					500						505						510
Gln	Lys	Asp	Val	Cys	Leu	Pro	Lys	Ala	Xaa	His	Gln						

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1075 1080 1085
Lys Ala Glu Thr Glu Asn Ser
1090 1095

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<210> 494
<211> 743
<212> PRT
<213> Homo sapiens
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<220>  
<221> variant  
<222> (1)...(743)  
<223> Xaa = Any amino acid
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Met	Lys	Leu	Leu	Met	Val	Leu	Met	Leu	Ala	Ala	Leu	Ser	Gln	His	Cys
				5					10					15	
Tyr	Ala	Gly	Ser	Gly	Cys	Pro	Leu	Leu	Glu	Asn	Val	Ile	Ser	Lys	Thr
			20					25					30		
Ile	Asn	Pro	Gln	Val	Ser	Lys	Thr	Glu	Tyr	Lys	Glu	Leu	Leu	Gln	Glu
		35					40					45			
Phe	Ile	Asp	Asp	Asn	Ala	Thr	Thr	Asn	Ala	Ile	Asp	Glu	Leu	Lys	Glu
	50					55					60				
Cys	Phe	Leu	Asn	Gln	Thr	Asp	Glu	Thr	Leu	Ser	Asn	Val	Glu	Val	Phe
	65				70					75					80
Met	Gln	Leu	Ile	Tyr	Asp	Ser	Ser	Leu	Cys	Asp	Leu	Phe	Met	Ser	Pro
				85					90					95	
Ala	Lys	Glu	Thr	Ser	Glu	Lys	Phe	Thr	Trp	Ala	Ala	Lys	Gly	Arg	Pro
			100					105					110		
Arg	Lys	Ile	Ala	Trp	Glu	Lys	Lys	Glu	Thr	Pro	Val	Lys	Thr	Gly	Cys
		115					120					125			
Val	Ala	Arg	Val	Thr	Ser	Asn	Lys	Thr	Lys	Val	Leu	Glu	Lys	Gly	Arg
	130					135					140				
Ser	Lys	Met	Ile	Ala	Cys	Pro	Thr	Lys	Glu	Ser	Ser	Thr	Lys	Ala	Ser
145					150					155					160
Ala	Asn	Asp	Gln	Arg	Phe	Pro	Ser	Glu	Ser	Lys	Gln	Glu	Glu	Asp	Glu
			165					170						175	
Glu	Tyr	Ser	Cys	Asp	Ser	Arg	Ser	Leu	Phe	Glu	Ser	Ser	Ala	Lys	Ile
			180					185					190		
Gln	Val	Cys	Ile	Pro	Glu	Ser	Ile	Tyr	Gln	Lys	Val	Met	Glu	Ile	Asn
		195					200					205			
Arg	Glu	Val	Glu	Glu	Pro	Pro	Lys	Lys	Pro	Ser	Ala	Phe	Lys	Pro	Ala
	210					215					220				
Ile	Glu	Met	Gln	Asn	Ser	Val	Pro	Asn	Lys	Ala	Phe	Glu	Leu	Lys	Asn
225					230					235					240
Glu	Gln	Thr	Leu	Arg	Ala	Asp	Pro	Met	Phe	Pro	Pro	Glu	Ser	Lys	Gln
			245						250					255	
Lys	Asp	Tyr	Glu	Glu	Asn	Ser	Trp	Asp	Ser	Glu	Ser	Leu	Cys	Glu	Thr
			260					265					270		
Val	Ser	Gln	Lys	Asp	Val	Cys	Leu	Pro	Lys	Ala	Thr	His	Gln	Lys	Glu
		275					280					285			
Ile	Asp	Lys	Ile	Asn	Gly	Lys	Leu	Glu	Glu	Ser	Pro	Asn	Lys	Asp	Gly
	290					295					300				
Leu	Leu	Lys	Ala	Thr	Cys	Gly	Met	Lys	Val	Ser	Ile	Pro	Thr	Lys	Ala
305					310					315					320
Leu	Glu	Leu	Lys	Asp	Met	Gln	Thr	Phe	Lys	Ala	Glu	Pro	Pro	Gly	Lys
			325						330					335	
Pro	Ser	Ala	Phe	Glu	Pro	Ala	Thr	Glu	Met	G					

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```

Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp
 370          375          380
Ser Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro
385          390          395          400
Lys Ala Xaa His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu
          405          410          415
Gly Ser Pro Val Lys Asp Gly Leu Leu Lys Ala Asn Cys Gly Met Lys
          420          425          430
Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met Gln Thr Phe
          435          440          445
Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu
          450          455          460
Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln
465          470          475          480
Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp
          485          490          495
Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr Val Ser
          500          505          510
Gln Lys Asp Val Cys Leu Pro Lys Ala Xaa His Gln Lys Glu Ile Asp
          515          520          525
Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asp Asn Asp Gly Phe Leu
          530          535          540
Lys Ala Pro Cys Arg Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu
545          550          555          560
Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser
          565          570          575
Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala
          580          585          590
Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Gln Met Phe Pro
          595          600          605
Ser Glu Ser Lys Gln Lys Xaa Val Glu Glu Asn Ser Trp Asp Ser Glu
          610          615          620
Ser Leu Arg Glu Thr Val Ser Gln Lys Asp Val Cys Val Pro Lys Ala
625          630          635          640
Thr His Gln Lys Glu Met Asp Lys Ile Ser Gly Lys Leu Glu Asp Ser
          645          650          655
Thr Ser Leu Ser Lys Ile Leu Asp Thr Val His Ser Cys Glu Arg Ala
          660          665          670
Arg Glu Leu Gln Lys Asp His Cys Glu Gln Arg Thr Gly Lys Met Glu
          675          680          685
Gln Met Lys Lys Lys Phe Cys Val Leu Lys Lys Lys Leu Ser Glu Ala
          690          695          700
Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln
705          710          715          720
Glu Leu Cys Ser Val Arg Phe Leu Thr Leu Met Lys Met Lys Ile Ile
          725          730          735
Ser Tyr Met Lys Ile Ala Cys
          740

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<210> 495

<211> 410

<212> PRT

<213> Homo sapiens

<400> 495

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Met Lys Leu Leu Met Val Leu Met Leu Ala Ala Leu Ser Gln His Cys
          5          10          15
Tyr Ala Gly Ser Gly Cys Pro Leu Leu Glu Asn Val Ile Ser Lys Thr
          20          25          30
Ile Asn Pro Gln Val Ser Lys Thr Glu Tyr Lys Glu Leu Leu Gln Glu
          35          40          45

```

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Phe Ile Asp Asp Asn Ala Thr Thr Asn Ala Ile Asp Glu Leu Lys Glu
 50 55 60
 Cys Phe Leu Asn Gln Thr Asp Glu Thr Leu Ser Asn Val Glu Val Phe
 65 70 75 80
 Met Gln Leu Ile Tyr Asp Ser Ser Leu Cys Asp Leu Phe Met Gly Thr
 85 90 95
 Arg Ala Leu Gln Cys Glu Val Ser His Thr His Glu Asn Glu Asn Tyr
 100 105 110
 Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys
 115 120 125
 Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys Glu Asn Lys
 130 135 140
 Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala Glu Leu Gln
 145 150 155 160
 Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg Ala Ser Gln
 165 170 175
 Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr Met Leu Thr
 180 185 190
 Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu Ala Glu Ile
 195 200 205
 Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp His Asp Gln
 210 215 220
 Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His Ile Ala Gly
 225 230 235 240
 Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser Ser Thr Ile
 245 250 255
 Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala Gln Arg Lys
 260 265 270
 Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp Ala Leu Arg
 275 280 285
 Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln Arg Glu Thr
 290 295 300
 Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn Glu Gln Asp
 305 310 315 320
 Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp Gln Lys Leu
 325 330 335
 Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln Leu Val His
 340 345 350
 Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile Asp Ile His
 355 360 365
 Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu Lys Asn Glu
 370 375 380
 Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile Tyr Gln Tyr
 385 390 395 400
 Glu Lys Glu Lys Ala Glu Thr Glu Val Ile
 405 410